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Award Number:
W81XWH-08-1-0148

TITLE
Acute Lung injury: Making Injured Lungs Perform Better and Rebuilding Healthy Lungs.

PRINCIPAL INVESTIGATOR:
Alan Fine, MD

CONTRACTING ORGANIZATION:
Boston Medical Center Corporation
Boston, MA 02118

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Fort Detrick, Maryland 21702-5012

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Alan Fine, MD

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Boston Medical Center Corporation

Boston, MA 02118

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
Acute lung injury (ALI) is a complex condition associated with diffuse injury to the alveolar epithelial gas exchange surface, resulting in marked impairment in the ability to oxygenate blood. The goal of our application is to develop ventilatory and cell based strategies to treat the ALI syndromes that complicate cancer care. As we have previously noted, ALI is associated with severe infections, exposure to toxins, trauma, and multiple blood transfusions. Cancer patients are particularly vulnerable to development of ALI as a result of the immunosuppressive effects of chemotherapy and the debilitating effects of cancer. Of note, military personnel are also at risk for development of ALI because of battle induced trauma and the consequent need for blood transfusions. In Project 1, we proposed to develop a novel mode of ventilation (variable ventilation) that will minimize the toxic effects of conventional mechanical ventilation in patients with ALI. We have completed various types of in vitro and in silico analysis of variable ventilation, and a result, are nearly ready to commence a clinical study. In the preclinical Project 2 study in mice, we have been optimizing the derivation of progenitor cells that can be administered to mice with ALI with the intent of reconstituting the damaged gas exchange surface. Our data suggest that iPS may be most suitable for this purpose. To summarize in the past year, we have: 1) successfully developed the necessary software for variable ventilation 2) continued the process of submitting an IND application to begin a Phase I study of variable ventilation, 2) and optimized derivation of mouse stem cells for testing in mice with ALI.

15. SUBJECT TERMS
Lung injury, cancer, ventilator, stem cells

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Introduction

The goal of our application is to develop strategies to treat the acute lung injury syndromes that complicate cancer care (ALI). As we have discussed, ALI occurs in a variety of clinical settings. These include: severe infections, exposure to toxins, trauma, and multiple blood transfusions. Caner patients are particularly vulnerable to development of ALI as a result of the immunosuppressive effects of chemotherapy and the debilitating consequences of cancer on overall well-being. Further, patients with cancer receive chemotherapeutic agents, which themselves can cause diffuse lung injury. The pathology of ALI is very complex but a salient features is diffuse injury to the alveolar epithelial gas exchange surface, resulting in marked impairment in the ability to oxygenate blood. In particular, type I cells, which comprise the vast majority of the gas exchange surface are particularly susceptible to injury. To meet our goal, this grant has 2 Projects. In Project 1, we proposed to build upon findings from animal studies to determine the optimal method for mechanical ventilation of patients with ALI. The critical need for better modes of ventilation derives from collected observations demonstrating that current ventilatory modalities may actually worsen underlying ALI. Specifically, we proposed to evaluate the efficacy of so-called *variable ventilation* in patients with ALI relative to conventional ventilation. In Project 2 of this proposal, our goal is to develop a cell based therapy with the intent of reconstituting the alveolar gas exchange surface. One important component of this Project is the development of appropriate and scalable cell populations that can be used for these purposes. As planned, a major part of this strategy is the use of a stem cell population, derived from embryonic stem cells, which are skewed towards lung epithelial differentiation. This is a pre-clinical study that uses laboratory mice, mouse cells, and a well-described model of chemotherapy induced ALI. In this report, I will discuss the progress made in these 2 Projects.

Body of Progress Report

Below is a summary of the progress and achievements for the 2 Projects that comprised the original parent proposal.

Project 1: We will determine if variable ventilation is a more effective mode of ventilation in patients with ALI.

During year two of this project, we identified and fixed a potential limiting engineering issue. This involved the integrity and reliability of the interface between the controlling study laptop computer and the ventilator that will deliver a variable ventilation mode. To resolve this issue, we collaborated with the ventilator manufacturer, *Covidien*. Our objective was to identify a solution that will permit careful modulation and monitoring of variable ventilation when administered to human patients. This necessarily required us to re-visit the variable ventilation software, itself, and to develop a new interface between the variable ventilation program and the ventilator.

Fortunately, the partnership between *Covidien* and the BUMC investigators resulted in re-engineered ventilator operating system software that will now enable the computer to run the variable ventilation program safely. This process necessitated the development of a legal agreement between us and *Covidien*, which is in the final stages of approval. We are currently testing the performance of the variable ventilation mode. This is being done through rigorous testing of the safety and accuracy of ventilatory functions in the variable mode using surrogate inanimate subjects. During this time, we have continued to write the FDA IDE document.

Dr. Bela Suki and his research team have completed a manuscript on a computer *in silico* simulation analysis of human alveolar mechanics using this updated software system. This will be submitted shortly.

It is our expectation that these testing steps will be complete by August 1, 2010. We are operating under the assumption that patient enrollment for this study will commence between September and October 2010. In anticipation, we have begun intensive training sessions with our clinical and research staff to improve compliance with ARDS Net low-tidal-volume-strategy ventilation, which is the control arm of this study.

A protocol is being developed to analyze the spontaneous variability in tidal volumes that are associated with current ventilatory modes. This work will enable meaningful comparisons in our variable ventilation study.

Project 2: We will establish a pre-clinical program conducted in laboratory mice with the objective of developing cell-based treatments for ALI.

The long-term goal of this project is to develop an autologous cell-based therapy to reconstitute the injured lung epithelium. A key element of this work is to evaluate and identify the optimal exogenous progenitor cell population with lung epithelial reparative properties. Since the start of this project, we have expanded our aims to include a newly discovered type of pluripotent stem cell, termed iPS cells, in addition to the originally proposed studies utilizing embryonic stem (ES) cells.

Based on our work in previous years deriving endodermal and lung progenitors from mouse ES cells, we turned our attention over the past year to testing whether this approach could be adapted to

the novel type of pluripotent stem cell recently discovered, termed induced pluripotent stem (iPS) cells. Our focus was on developing new reprogramming approaches to derive iPS cells from mice and humans. The primary advantages of iPS cells are that they are easily derived, highly scalable, and since they can be readily derived from individual mice (or humans) they thereby circumvent immune and ethical issues.

.At this point we have been reprogramming fibroblasts into iPS cell lines. Cre/lox mediated excision of the reprogramming vector has been completed with stability of karyotype and characterization completed of these iPS cell clones in the undifferentiated state. We have observed that: 1) 90% of clones generated with this system are reprogrammed with a single copy of integrated lentivirus (STEMCCA-loxP) encoding the 4 reprogramming transcription factors, Oct4, Sox2, Klf4, and cMyc, 2) the vector can be simply excised with cre-mediated vector excision with stability of phenotype and karyotype, 3) the resulting clones are pluripotent based on marker gene staining, RT-PCR profiling, and teratoma assays.

We have also begun endodermal differentiation of the resulting iPS cell clones and find that endodermal differentiation is intact in these clones following the cre-mediated excision of reprogramming transgenes. Endodermal differentiation is the first step towards lung epithelial differentiation. Thus, understanding these processes is key for our cell based strategy.

In addition, to evaluate the genetic programs of iPS cells undergoing endodermal differentiation, we performed microarray experiments using our existing bank of mouse iPS cells. We screened for differences between ES and iPS cells both in the undifferentiated state as well as after endodermal differentiation. These studies found that ES and iPS cells in both states differ by only a few transcripts localized to the Dlk1-Dio3 imprinted gene cluster on chromosome 12. There is aberrant silencing of maternally inherited genes in this cluster in iPS cells and these genes remain silent during endodermal differentiation, even though the genes are induced during endodermal differentiation in control mouse ES cells. We are now focused on determining whether this pattern of aberrant silencing of this gene cluster in human iPS cells is also detectable, or whether this phenomenon is exclusive to mouse iPS cells. A manuscript has been submitted detailing these microarray experiments and findings. These findings are being extended into our work on mouse iPS cells and will be relevant to identifying the most effective cell source for reconstituting a damaged alveolar epithelium.

Several teams have noted that vector-based reprogramming is often ‘incomplete’ resulting in a significant number of ‘partially reprogrammed’ iPS clones, which can be distinguished from fully reprogrammed clones on the basis of marker gene expression. We found all clones generated with the STEMCCA-loxP vector expressed a broad complement of ‘stem cell markers’ including those previously reported to be absent in ‘partially reprogrammed’ clones, such as Tra1-60, Rex1 and DNMT3B. We speculate that the majority of those clones reported as partially reprogrammed in other studies may have arisen from cells that either did not receive all reprogramming factors or expressed the factors with stoichiometries or expression levels that did not allow for complete reprogramming. Since most clones generated with the STEMCCA-loxP vector received a single copy of all 4 reprogramming factors, partial reprogramming may be minimized, potentially explaining why our results contrast with those of prior studies using multi-vector approaches.

Our results indicate that iPS and ES cells undergo directed differentiation to definitive endoderm with induction of remarkably similar local and global gene expression programs. The key pioneer factors and transcriptional regulators known to be important in definitive endoderm development, such as Foxa2, Gata4/6, and Sox17 are all similarly upregulated during endodermal directed differentiation of ES and iPS cells, and the waves of marker genes (e.g. Afp and albumin) expressed during subsequent lineage specification of ES and iPS-derived endoderm also follows a sequence that has been described in the developing embryo. Beyond these specific individual genes, our results indicate significant overlap in the global gene expression programs of definitive endoderm precursors derived *in vitro* from pluripotent stem cells compared to embryonic definitive endoderm from the developing mouse embryo. Endodermal derivatives, may in fact be most suitable for cell based therapy.

We found ES and iPS cells, at least in the mouse model system, do differ significantly in the expression levels of other genes encoded or targeted by transcripts normally expressed from the imprinted Dlk1-Dio3 gene cluster. Aberrant imprinting of this gene cluster in the vast majority of mouse iPS cell lines in the undifferentiated state was recently described and was found to correlate with impaired functional capacity of iPS cells to form 'all-iPS derived mice' after transplantation into 4n blastocysts. While genes in this cluster have also been reported to have functional roles in mouse development, we found surprisingly intact capacity of aberrantly imprinted iPS cells to undergo directed differentiation into definitive endoderm *in vitro*. This is in marked contrast to recent observations of a reduced capacity of human iPS cell lines to undergo directed neuronal directed differentiation, compared to ES cells. Since the iPS cell-derived early hepatic lineages that co-express Afp and albumin in our studies correlate roughly to E8.5-10.5 in the mouse embryo, this developmental stage may be too early to detect defects in iPS cell-derived liver cells. Indeed liver abnormalities in mice with deletions of maternally-inherited Gtl2 genes were only evident post-natally, and in mice with uni-parental paternal disomy of distal chromosome 12, lethality was only evident at midgestation. Although, the aberrantly imprinted iPS cells in our studies were able to contribute efficiently to E11.5 mouse chimeras after blastocyst transplantation, displayed germ-line competence, and formed chimeric post-natal mice with high coat color chimerism and grossly normal chimeric lungs and livers; it remains possible that a detailed evaluation of mature endodermal tissues *in vivo* might reveal more subtle abnormalities of iPS-derived endodermal epithelia.

Overall our results have considerable implications for those wishing to develop cell-based therapies to reconstitute diseased endodermal-derived tissues, such as the lung during ALI.. Regardless of imprinted status, iPS cells can be differentiated efficiently into definitive endoderm precursors using the same serum-free culture protocols developed to derive endoderm from ES cells. As with ES cells, flow cytometry-based sorting algorithms can be devised to both reduce heterogeneity of iPS-derived populations and to reduce the presence of undifferentiated cells expressing residual Nanog or Rex1. Following this rigorous assessment and optimization of derivation of mouse iPS and embryonic stem cells, we are now uniquely positioned to evaluate their therapeutic efficacy in mouse models of ALI.

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Key Research Accomplishments

● Identified and resolved software issues regarding the interface between the variable ventilation program and the ventilator.

● Continued refinement of the FDA IDE application

● Maintained Institutional Review Board approval of Phase I variable ventilation study.

● Continued to work with clinical and research staff to improve compliance with the study's control arm.

● Manuscript ready for submission on *in silico* analysis of variable ventilation.

● Optimization of iPS cell derivation for cell based therapy

● Clarification of genetic differences between iPS and embryonic stem cells

● Banking of iPS cells for future use

● Manuscript submitted on genetic differences between iPS and embryonic stem cells

Reportable Outcomes

1) Delineation of clinical grade mouse iPS cells for ALI treatment

2) Publication of manuscript on in silico analysis of variable ventilation

3) Publication of manuscript on imprinted genetic differences between iPS and ES cells

4) Final approval of IND for variable ventilation

5) Patient recruitment and initiation of variable ventilation study in human patients

6) Injection of clinical grade iPS cells into mice subjected to ALI.

7) Approval of legal agreement with *Covidien* on ventilator software

Conclusion

We have made considerable progress in both Projects of the original parent grant. For Project 1, we have been focused on ensuring the safety and efficacy of the interface software required for administration of variable ventilation. This is a key hurdle that needs to be confidently resolved in order to complete our IND application and to initiate our clinical study. To resolve this issue, we collaborated with the ventilator manufacturer, *Covidien*. This partnership resulted in a re-engineered ventilator operating system software that will now enable the computer to run the variable ventilation program safely and efficiently. We are currently testing the performance of the variable ventilation mode software using surrogate inanimate subjects. During this time, we have continued to write the FDA IDE document.

In Project 2, we have continued to optimize the derivation of stem cell preparations for delivery to mice with ALI. In this work, we have been able to identify differences between iPS and embryonic mouse cells that theoretically could be of clinical import. We are focused on understanding the molecular factors that control differentiation of these cells into lung epithelium; this should further bolster and enhance our ability to develop a rational strategy for reconstituting the damaged alveolar epithelial surface in ALI.

APPENDIX

Title of Study:	VARIABLE VENTILATION IN ACUTE LUNG INJURY
Protocol Number:	H-27864
RE:	Contining Review
Review Type:	Expedited
Action:	Approved
Date of Action:	3/19/2010
Date of Expiration:	3/18/2011
Funding Source:	Government: Department of Defense Award# W81XWH-08-1-0148 BUMC Source #057-298-5880-8: we will forward grant to IRB, it is too large to attach in INSPIR Government Award #: W81XWH-08-1-0148
BMC AU # or Record #:	5880-8

Dear GEORGE O'CONNOR, MD:

The Institutional Review Board (IRB) has reviewed the above referenced protocol and has determined that it meets the requirements set forth by the IRB and is hereby approved. This protocol is valid through the date indicated above.

Revisions have been reviewed and approved as of this date 3/22/10.

The study may not continue after the approval period without additional IRB review and approval for continuation. You will receive an email renewal reminder notice prior to study expiration; however, it is your responsibility to assure that this study is not conducted beyond the expiration date.

Please be aware that only IRB-approved informed consent forms may be used when informed consent is required. Only consent forms validated with current approval dates (either generated by the INSPIR system or by a manual stamp by the IRB office) may be used. Manually stamped consent forms may be found under External Attachments in INSPIR.

Any changes to the protocol or informed consent must be reviewed and approved prior to implementation unless the change is necessary for the safety of subjects. In addition, you must report to the IRB unanticipated problems involving risk to subjects or others according to the process posted on the IRB website. The IRB must be informed of any new or significant information that might impact a research participant's safety or willingness to continue in your study.

Investigators are required to ensure that all HIPAA requirements have been met prior to initiating this study. Once approved, validated HIPAA forms may be found within INSPIR as External Attachments.

It is the responsibility of the PI to ensure that all required institutional approvals have been obtained prior to initiating any research activities.

Please note that the IRB is no longer stamping attachments, subject letters, recruitment materials, etc. These documents are each associated with this approved version of the protocol. They can be found by going to Letters/Protocol History in INSPIR and clicking on the highlighted (linked) word "Approved" and then clicking on the paperclip icon in the upper left corner. *This does NOT apply to consent forms, which must be validated.

-

Sincerely yours,

ELIANA MEIROWITZ
IRB Board Member

Institutional Review Board

Status: Approved
Initial Submit Date: 3/17/2009
Approval Period: 3/19/2010 - 3/18/2011

Section Aa: Title & PI

Protocol Number: H-27864

A1. Protocol Title: VARIABLE VENTILATION IN ACUTE LUNG INJURY

A2. Principal Investigator

ID: 502787
Name: GEORGE O'CONNOR Title: MD
School: MEDICINE (MED)
Department: PULMONARY CENTER
Section: PULMONARY CENTER
CRC Center: None
Location: 715 Albany Street, R-304, Boston, MA 02118 Phone: (617) 638-4470
E-mail: GOCONNOR@BU.EDU Fax: [FAX]
Did this person identify a conflict of interest?: No

A3. PI's Administrative Contact

None

A3b. IRB Authorization Agreement (IAA)

Is there an IAA (IRB Authorization Agreement) for this protocol? Yes
If yes, please select the appropriate Institution(s) / Agreement(s) type:
BU-Charles River Campus

Section Ab: General Information

A4. Co-Investigators / Study Personnel

ID: 502548
Name: ARTHUR THEODORE
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Department: PULMONARY CENTER
Section: PULMONARY CENTER
CRC Center: None
Location: Phone: (617) 638-4933
E-mail: ATHEODOR@BU.EDU Fax: [FAX]
Role in Study: Co-investigator
Did this person identify a conflict of interest?: No
Is this person an employee of BU, BMC, Boston Public Health Commission (BPHC) or a Boston Healthnet Community Health Center (CHC)?: Yes

ID: 520137
Name: ALLAN WALKEY
Title: MD

School: MEDICINE (MED)
Department: PULMONARY CENTER
Section: PULMONARY CENTER
CRC Center: None
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E-mail: ALWALKEY@BU.EDU Fax: 617-536-8093
Role in Study: Co-investigator
Did this person identify a conflict of interest?: No
Is this person an employee of BU, BMC, Boston Public Health Commission (BPHC) or a Boston Healthnet Community Health Center (CHC)?: Yes

ID: 520657
Name: CHARLES O'DONNELL
Title: RRT
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Department: MEDICINE
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CRC Center: None
Location: Phone: 617 638 6126
E-mail: CHODONNE@BU.EDU Fax: [FAX]
Role in Study: co-investigator
Did this person identify a conflict of interest?: No
Is this person an employee of BU, BMC, Boston Public Health Commission (BPHC) or a Boston Healthnet Community Health Center (CHC)?: Yes

ID: No INSPIR Access
Name: BELA SUKI

Institution: Boston University
Location: School of Biomedical Engineering Phone: 617-353-5907
E-mail: bsuki@bu.edu Fax:
Non-BUMC Researcher Info: Bela Suki, PhD is a Professor of Biomedical Engineering here at BU. He holds the patent for the mode of variable ventilation we will be using in this study. He will provide the programs for running this ventilator mode in a standard Puritan-Bennett 840 ventilator as well as provide support for measurements of lung physiology and mechanics. He will not be involved in any subject evaluation, consent, or treatment activities.
Role in Study: co-investigator
Did this person identify a conflict of interest?: Yes
Is this person an employee of BU, BMC, Boston Public Health Commission (BPHC) or a Boston Healthnet Community Health Center (CHC)?: Yes

ID: No INSPIR Access
Name: ARNAB MAJUMDAR

Institution: BU
Location: Biomedical Engineering Phone: 617-353-5907
E-mail: arnab@bu.edu Fax:
Non-BUMC Researcher Info: Arnab is a PhD post-doctoral fellow working with Professor Suki in the design and programming of the variable ventilation mode. He will not be involved in any subject evaluation, consent, or treatment activities.
Role in Study: co-investigator
Did this person identify a conflict of interest?: No
Is this person an employee of BU, BMC, Boston Public Health Commission (BPHC) or a Boston Healthnet

Community Health Center (CHC)?: Yes

A5a. Funding Source

Government: Department of Defense Award# W81XWH-08-1-0148 BUMC Source #057-298-5880-8: we will forward grant to IRB, it is too large to attach in INSPIR
Government Award #: W81XWH-08-1-0148
Government PI of Award: George O'Connor

Grants Office:
BMC Grants Administration (OGA)
BMC AU # or Record #: 5880-8

Funding Notifications:
N/A

ARRA Award:
N/A

A5b. Conflict of Interest Disclosure

Have all investigators and staff in this study submitted COI Forms? Yes

On the submitted Conflict of Interest Disclosure forms, have you or any of your research staff identified a significant financial interest? Yes

A6a. Institution(s) where work will be performed in the U.S.

Boston University Medical Center
List below all other U.S. sites where study activities will take place.
Boston Medical Center

A6b. Non-US Sites Under Supervision of BU/BUMC PI

(NONE)
Facility, institution, and FWA numbers:

Section B: Review Path Determination

Does this study involve greater than minimal risk to the subject? Yes

B1. Exempt From IRB Review

Not Applicable

B1a. Non-Human Subjects Research

Not Applicable

Not Applicable

B2. Expedited Review

If this is a drug study, is an investigational new drug (IND) application required? N/A

If this is a device study, is an investigational device exemption (IDE) application required? N/A

If this study involves blood collection from healthy, non-pregnant subjects who weigh at least 110 pounds, will you

be drawing less than 550 ml in an 8 week period and collections not more frequent than twice per week? N/A

If this study involves blood drawing from other adults or children (considering age, weight, and health of the subjects), will you be drawing less than 50 ml or 3ml/kg and collections not more frequent than twice per week? N/A

If the study involves collection of other biological samples, will the samples be collected by non-evasive means (e.g. hair samples, extracted teeth, urine, stool, saliva, placentas collected during delivery, and mucosal cells collected by scraping or swab)? N/A

Will the research data in this study be gathered through non-invasive means used routinely in clinical practice (excluding x-ray or microwave studies and procedures performed under sedation or anesthesia)? N/A

Will the research data in this study come from materials (documents, records, specimens) that have been or will be collected for non-research related purposes (e.g., in the course of medical treatment or diagnosis)? N/A

Will the research data in this study come from voice, digital, video, or image recordings made for research purposes? N/A

Does the research involve individuals or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies? N/A

Does the research involve pedigree studies or collection or storage of samples for genetic analysis? No

Does the research involve any types of data, samples, or collection methods not mentioned in the questions above? No

B3. Compassionate/Emergency Use

Is this an compassionate/emergency use situation? No

Section C: Study Summary

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) respresent a spectrum of clinical syndromes of rapid respiratory system deterioration that are associated with both pulmonary and systemic illness. These syndromes are associated with 30-40% mortality with our current standard of care and are responsible for approximately 75,000 deaths in the US yearly. The current standard of care is a strategy of mechanical ventilation utilizing low lung volumes intended to limit further lung injury induced by the ventilator. However, the single lung volume delivered in the low tidal volume strategy is not consistent with the variability in respiration of healthy humans, has been shown to contribute to increased lung injury in some studies, and still results in 30-40% mortality rates. Recent studies of ARDS animal models by BU Professor Bela Suki and others have shown that varying the lung volume and respiratory rate delivered by a ventilator significantly decreases biomarkers of lung injury, improves lung mechanics, and increases oxygenation when compared to identical mean volumes of conventional, monotonous low lung volume ventilation. We propose a first-in-human, Phase I study to evaluate the safety of this novel mode of ventilation, Variable Ventilation.

Section D: Background/Rationale/Purpose

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) respresent a spectrum of syndromes of severe lung inflammation resulting from both pulmonary and systemic disease. These syndromes have a 30-40% mortality with our current standard of care, a mechanical ventilation strategy which limits further lung injury ("ARDSNet low tidal volume"). However, this ARDSNet ventilation strategy removes the variability in respiration that occurs in a normal state of health. Multiple pre-clinical studies of ARDS models have demonstrated that adding variability to mechanical ventilation (Variable Ventilation) results in significant improvements in oxygenation, lung mechanics, and biomarkers of lung injury when compared with the current standard of care ventilation strategy. Proposed mechanisms for the improvements seen with Variable Ventilation involve increased secretion of the lung surfactant depleted in ALI/ARDS (1,2) and enhanced lung recruitment at lower, less injurious mean airway pressures (3-6). A different of variable ventilation method from what we plan to

study, based on the breathing patterns of a dog, has been tested in normal humans undergoing aortic surgery (3) and in six patients with ARDS (4). These studies have shown this method of variable ventilation to be safe and to improve oxygenation. Our method of variable ventilation, designed and tested in multiple pre-clinical animal studies (1-2,5-6) by BU Professor Bela Suki, utilizes mathematical modeling of lung mechanics to assign the ideal level of variation in humans. A full description of the pre-clinical evdidence supporting Variable Ventilation is attached in section S. The purpose of this study is to investigate in a Phase I trial the safety and efficacy of a short duration of the Suki method of Variable Ventilation in human subjects with ALI and ARDS. Our hypotheses are: 1) variable ventilation is safe; 2) variable ventilation will result in improved oxygenation, lung mechanics(such as lung compliance and lung dead space), and biomarkers of lung injury when compared with the standard of care mechanical ventilation strategy.

Section E: Protocol Risks/Subjects

E1. Risk Category

Category 2: Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects.

E2. Subjects

Gender: Both

Age: Adult (18-64 yrs), Geriatric (65+ yrs)

Ethnicity: All Ethnic Groups

Languages: English, Spanish

Groups to be recruited will include: Patients only

Vulnerable populations to be recruited as subjects: Cognitively Impaired

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

Informed consent will be obtained by the study coordinator/respiratory therapist from legally authorized representatives (defined as a subject's next of kin as defined by Massachusetts common law); study subjects with ALI/ARDS requiring mechanical ventilation are likey to be cognitively impaired due to pharmacological sedation and by severe illness. Undue coercion will be prevented by stressing during the consent process that particiaption is voluntary, lack of participation will not change future care, and that the purpose of the study is to assess safety of this ventilator mode. Subject confidentiality will be protected with the use of password-protected, coded, de-identified data sets only. Keys to decode the data will be kept only by the primary investigator in a locked drawer, separate from the data set. Study physicians will be available in person to answer any questions arising during the consent process.

Section F: Design/Procedure

F1. Design

Select one category that most adequately describes your research: Device, investigator-initiated, single center

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.

The design of this study is a within-subjects, randomized, crossover design. The randomized crossover design allows for control of known and unknown time- and order- dependent confounders (such as a tendency of a subject to improve over time). Additionally, it allows for better control of a placebo-type effect that might occur when a subject is being closely monitored in a study setting, as opposed to a case series setting. For example, a false positive efficacy result might be seen if patients tend to improve over time and variable ventilation always follows conventional ventilation in the protocol order. The crossover design eliminates this confounding. One prior randomized crossover study using a different method of variable ventilation (McCarthy BG et al ATS abstract 2009), with four hours per ventilator mode, did show statistically significant improvement in lung compliance and lung dead space, with a trend towards improved oxygenation, in nine ALI/ARDS subjects. The results of this study suggest that a prolonged carrover effect does not exist for the improvements seen with

variable ventilation. Lastly, in order to assess for any carryover effects, we will compare outcomes at the end of variable ventilation with the baseline values prior to starting variable ventilation, and compare the baseline conventional ventilation variables with the randomized crossover conventional ventilation values. These should be equal in the absence of a carryover effect.

Subjects will be enrolled only when 'stable' clinically. 'Stability' is defined in the inclusion criteria below. Clinically stable patients will then be randomized via concealed envelope to an order for crossover (50% chance of variable ventilation prior to conventional ventilation or conventional ventilation prior to variable ventilation).

Inclusion criteria

Inclusion criteria 1. Age > or equal to 18 2. Requires mechanical ventilation using a volume or pressure-controlled mode. 3. Admitted to Boston Medical Center Surgical, Medical, or Coronary Intensive Care Unit 4. Meets American-European Consensus Criteria for Acute Lung Injury (ALI) or Acute Respiratory Distress Syndrome (ARDS): 4a. Acute onset of respiratory compromise AND 4b. Bilateral frontal chest radiographic infiltrates AND 4c. PaO2/FiO2 ratio less than 300 for ALI, less than 200 for ARDS; or if no arterial blood gas has been drawn by the primary team, a SaturationO2/FiO2 ratio less than 315 for ALI or less than 235 for ARDS. 4d. No clinical sign of left atrial hypertension; or a known pulmonary wedge pressure less than 18mmHg 5. Meets "Clinical Stability Criteria" (on maximun of two vasopressor medications) for at least one hour prior to start of study protocol: 5a. Hemodynamically stable: mean arterial pressure greater than 60mmHg, heart rate greater than 50 and less than 130bpm 5b. Respiratory system stable: Respiratory rate less than 35 bpm, O2 saturation greater than 88%, peak pressure on ventilator less than 40mm H20, requires suctioning less than once hourly. 5c. Acid-base stability: pH greater than 7.2 and less than 7.55 5d. Neurologic system stable: No agitation as defined by Ramsay Sedation Score greater than or equal to 2 6. Had been requiring mechanical ventilator for less than 14days 7. Had met ARDS or ALI criteria for less than 7 days prior to enrollment 8. Assent of primary care team

Exclusion criteria

Exclusion Criteria 1. Do not resuscitate order 2. Increased Intracranial pressure 3. Pregnancy (urine pregnancy test for all women of child-bearing age) 4. Planned transport out of ICU during planned study protocol 5. Coagulopathy (INR>2.0 or PTT >50) 6. Severe thrombocytopenia (platelets <20,000)

F2. Procedure

Methods Eligible patients will be identified by the primary intensive care unit team, who will notify the study coordinator/respiratory therapist. The study coordinator is a registered respiratory therapist with human subjects research training and qualifications for obtaining consent, clinical monitoring, arterial blood drawing, and ventilator management. The study coordinator will explain the study in detail and clearly outline that the purpose of the study is to assess safety of the new ventilator mode, that benefit is possible but not guaranteed, and that treatment is not the purpose of the study. After consent is obtained from the potential subject's 'Legally Authorized Representative', the subject will begin the study protocol when all of the inclusion criteria are met. At this time a concealed envelope will be opened to reveal the order of ventilation strategies: either variable ventilation (VV) then conventional ventilation (CV), or vice versa. Each patient will be ventilated for three hours on each ventilator strategy. Baseline arterial blood samples for blood gas measurements and biomarkers of lung injury, as well as non-invasive lung mechanics (eg., lung compliance and lung dead space measurements) and hemodynamic measurements (eg., blood pressure, heart rate) will be performed 15 minutes prior to the initial study ventilator mode (BASELINE), and at time2h 45min (TIME ONE) of the intial ventilator mode (ie., the last 15 minutes of the intial ventilator mode), and at time 5h 45min (TIME TWO, the last 15minutes of the subsequent ventilator mode). After a total of six hours (three hours on each ventilator mode), the protocol will be complete and the patient will be returned to the ventilator settings he or she had been on prior to the study protocol. All subjects will be continuously monitored through the six hour study protocol by the study respiratory therapist and with continuous EKG, respiratory rate, blood pressure, and oximetry monitoring as per standard of ICU care. In addition, continuous exhaled CO2 monitoring will be utilized to assure adequate minute ventilation. After the six hour monitoring on both ventilator settings, the intervention will be complete. However, if a subject is randomized to the Variable Ventilation mode second, he or she will be followed for one hour after change back to the baseline ventilator mode for recording changes in vital signs and lung mechanics as described below. Additionally, subjects will be monitored for 24 hours after the protocol for the appearance of unanticipated or adverse events.

Definition of Conventional Ventilation (CV): Patients with ALI/ARDS in our BMC ICUs are ventilated per the current evidence-based standard of care for ARDS/ALI: the "ARDSNet" low tidal volume ventilator strategy. This will be the ventilator strategy that subjects will on be at study baseline and will function as the control: "Conventional Ventilation". A detailed description of the ARDSNet strategy is attached in the Supplement. Briefly, subjects are ventilated with a goal tidal volume of 6cc/kg ideal body weight , a goal plateau pressure of <30mmHg, and a goal respiratory rate of 6-35bpm to achieve a goal arterial pH of 7.30 to 7.45. PEEP is set as per

the ARDSNet PEEP table (see Supplement, low PEEP/higher FiO2 card).

Definition of Variable Ventilation (VV): Variable ventilation will be delivered through a standard Puritan-Bennett 840 ventilator (see Supplement for brochure). Briefly, a laptop containing the "Variable Ventilation" program will be attached to the ventilator to run the "Variable Ventilation" program for the three hour time period. This system is under review for Investigational device exemption from the FDA with IDE number (to be obtained). No patients will be enrolled until FDA IDE and IRB approval are given. Patients will be ventilated at a mean tidal volume to match their baseline tidal volume prior to study enrollment, however tidal volume will randomly vary by 30-40% on a breath by breath basis. Mean respiratory rate will then be set to achieve the minute ventilation that each subject had maintained prior to study entry. Similarly, this respiratory rate will be delivered with a 30-40% breath-to-breath variability.

Baseline Data Baseline demographics and clinical information including age, sex, APACHEII score, lung injury score, mean arterial blood pressure, heart rate, dose of vasopressors, platelet count, creatinine, O2 saturation, chest imaging findings, site of care, diagnosis, sedation score, dose of sedative medications, mode of ventilation and ventilator settings prior to protocol will be collected for each subject.

Safety Outcomes The primary outcome to be assessed is safety , as defined by comparison in each study group of: 1. Heart rate and blood pressure (measured via standard ICU monitors). Any heart rate or blood pressure lasting >30 seconds outside of the "clinical stability criteria" range will be recorded as an adverse event. Heart rate and blood pressure will also be recorded at Baseline, Time 1 and Time 2. 2. Occurrence of any 'serious adverse event', defined as a loss of any of the above-defined 'clinical stability criteria' as well as any of the following occurrences occuring during during the Variable ventilation phase or within one hour of change in ventilator strategy. Serious adverse events will be defined as: 3a. Hemodynamic instability requiring administration of new vasopressor or 100% increase in current vasopressor dose. 3b. Self-extubation 3c. Pneumothorax 3d. Decrease in O2 saturation greater than 8% or to less than 88% for more than 5 minutes 3e. Myocardial infarction 3f. Stroke 3g. Death 3. 24 hour protocol safety assessment: Subjects will be reassessed 24 hours after completion of the protocol for the potential of any delayed effects of partcipating in the study. No interventions or study blood draws will be performed. We will review the medical record and collect data that mirrors the collected baseline data: systolic /distolic blood pressure, heart rate, dose of vasopressors, platelet count, creatinine, O2 saturation, chest imaging findings, dose of sedative medications, mode of ventilation and ventilator settings. Additionally we will collect data on any adverse events occuring within the 24 hours after study completion.

Efficacy Outcomes Additionally, efficacy will be investigated, with the study powered to detect an increase in oxygenation (PaO2 in mmHg) from the "Conventional Ventilation" to the "Variable Ventilation" phase. Other secondary outcomes studied will be changes in sedation medications, lung mechanics, and biomarkers of lung injury with "Variable Ventilation" vs "ARDSNet" conventional ventilation. All comparisons (with exception of dose of sedatives) for efficacy will be between measurements performed at Time 1 and Time 2. Specifically, these measurements are: 4. Oxygenation: PaO2 in mmHg (from blood gas) and O2 saturation (from oximetry) 5. Ventilation: PaCO2 (from blood gas) 6. Physiologic pulmonary Dead space: amount of lung without adequate ventilation (Vd/Vt, measured non-invasively through volumetric CO2 NICO2 monitor) 7. Static lung compliance : ease of filling lung with air (Vt/change in pressure) measured with ventilator through 0.5s inspiratory hold 8. mean airway pressure (recorded noninvasively from ventilator) 9. peak airway pressure (recorded noninvasively from ventilator) 10. heart rate variability (calculated from non-invasive continuous EKG monitor) 11. plasma biomarkers of lung injury (IL-6, IL-8, sTNFa RI, IL1-r-a, SP-D), measured from arteral blood draw 12. Dose of sedative medications required during each mode (total dose during three hours).

Estimated Duration of Enrollment We estimate that 16 subjects will provide 80% power at an alpha =0.05 to detect a 25mmHg difference in PaO2 +/-25mmHg standard deviation at three hours. Our medical and surgical ICUs care for approximately ten ARDS/ALI patients monthly. If half of these patients eventually meet entry criteria and we have a 20% consent rate, then we should be able to enroll one patient monthly. Therefore, the study should last approximately 16 months.

Estimated Duration of the Study from IRB approval through data analysis and close of the study: Twenty four months.

Section G: Sample Size/Data Analysis

G1. Sample Size

How many subjects (or specimens, or charts) will be enrolled in this study?

Local: 16 Worldwide: 16

Please indicate why you chose the sample size proposed:

16 subjects participating in the protocol will provide 80% power at an alpha =0.05 to detect a within subject 25mmHg +/- 25mmHg difference in PaO2 between the study groups. An effect of this magnitude was seen in the two prior human studies of variable ventilation.

G2. Data Analysis

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study? If you are doing qualitative research please state how comparisons will be made.

This crossover Phase I study is meant to assess the safety and efficacy of a novel mode of mechanical ventilation for human ARDS/ALI. The safety endpoint, the occurence of serious adverse events defined as loss of 'clinical stability' criteria or predefined serious adverse event, is a categorical yes/no variable and will be analyzed with McNemar's test. Wilcoxon signed rank tests will be used for efficacy endpoints which involve clinical measurements of continuous variables which may or may not have a normal distribution, given the small smaple size (PaO2, compliance, heart rate, blood pressure, dead space). Prior studies have shown that the biomarkers of lung injury we plan study are usually nonparametrically disctributed, therefore Wilcoxon signed rank tests will also be used for differences and results wil be reported as medians and interquartile range. An alpha level of 0.05 will determine statistical significance.

Section H: Potential Risks/Discomforts

List the possibilities for risk or harm to the subjects as a result of their participation in the research, including discomforts, hazards, or inconveniences to the subject. Indicate what measures will be taken to prevent or to minimize the effects of hazards, discomforts or inconveniences. Include a detailed description of your Data Safety Monitoring Plan (DSMP).

This is a Phase I study of a novel method of mechanical ventilation called Variable Ventilation. This method of ventilation is provided through the standard mechanical ventilator used in the BMC ICU (Puritan-Bennett 840) which has been modified to run a program via laptop computer that randomly varies tidal volume and respiratory rate. This modified ventilator will be studied with an FDA Investigational Device Exemption and labeled as experimental use only. The ventilator will retain all funtionality of its unmodified version, plus the ability to run the custom variable ventilation program.

The primary risks of this study are similar to the potential risks associated with mechanical ventilation, a change in ventilator mode, and with arterial blood drawing in general. Risks of mechanical ventilation and changing ventilator modes include, but are not limited to, patient agitation, self-extubation, pneumothorax, airway collapse/mucus plugging, hypotension, arrhythmia, stroke, myocardial infarction or death. Additionally, unforseen device malfunction or patient intolerance of the device are potential risks of any new device. Given that this device is a slight modification to a standard ventilator, we expect the probability of either occurence to be low. Additionally, prior studies (references 3,4 see section S) of a different method of variable ventilation in human subjects have not shown an increase in adverse events with variable ventilation. Patients will be monitored continuously by a clinically trained study coordinator/registered respiratory therapist who will supervise all patients through their study protocol session. If at any time a device malfunction might occur, a subject will be immediatley placed back on their pre-study ventilator mode and the primary team, as well as the PI, will be notified. Enrollment will be suspended until any malfunction is fully corrected. If any 'clinical instability' criterion or serious adverse event criteria are met, the study session for that patient will be suspended, the primary care team and PI will be notified, and the subject will be returned to the baseline ventilator mode used prior to the study protocol.

Some subjects in this study will have pre-existing arterial catheters for arterial blood drawing as part of their usual clinical care. For these subjects, risks of non-invasively drawing a total of 9ml (3ml x 3 draws) of blood over 6 hours are minimal. Subjects without pre-existing arterial catheters will have arterial puncture performed for blood drawing. This procedure is routinely performed in the ICU without the need for informed consent. No study has investigated the complication rate for arterial puncture alone, which would be expected to be lower than the complication rates for long-term, in-dwelling arterial catheters. For long-term, in-dwelling arterial catheters, complication rates are: Permanent ischemic damage (0.09%), pseudoaneurysm (0.09%), sepsis (0.13%), local infection (0.72%), hematoma (14%), temporary arterial occlusion (19%) (Scheer et al Critical Care 2002, 6:198-204). Skin will be prepared in a sterile manner and injected with 1-2cc of 1% lidocaine for local anesthesia prior to arterial puncture. There is a risk of transient, local discomfort during the lidocaine injection.

DATA SAFETY MONITORING PLAN (also attached in S) Risk

Given the natural history patients with ALI/ARDS, there is a moderate likelihood that 'clinical instability' may occur by chance in any patient, therefore this study is classified as high risk. In order to allow for optimal safety monitoring and control of risk, only one patient will be enrolled at a time, exposure to the new ventilator mode will be limited to three hours, and patients will be monitored continuously by the study respiratory therapist as well as the clinical care team with clear stopping rules in place (see below). Additionally, all adverse events will be recorded regardless of supposed relationship to the intervention, and two independent monitors will assess individual events as well as events in aggregate to determine trends.

Internal Data Monitoring

The PI has overall responsibility for this study, however, sub-investigators with professional clinical training will also have subject monitoring responsibilities. The sub-investigators will conduct real-time data safety monitoring and report to the PI. The sub-investigators include the study coordinator/respiratory therapist and senior pulmonary/critical-care fellow Allan Walkey, MD.

External Data Monitoring

Safety monitoring of this study will be performed by an independent two-member Safety Committee comprised of two attending critical care specialists from the BUMC Surgical and Anaesthesia Critical Care Division. These monitors, while experts in critical care, are not investigators associated with this study or the clinical division conducting the study.

Unanticipated Problems

We will utilize the BUMC definition of unexpected problems: as an event that is unexpected in severity, nature or frequency given the research procedures and the characteristics of the subject population, related or possible related to participation in the research, and suggests that research places subjects at a greater risk of harm related to the research than was previously known or recognized.

Adverse Events

We will utilize the BUMC definition of Adverse events: any untoward or unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. These will be graded as mild=not requiring treatment, or serious=requiring a change in care or treatment. As a guideline, the occurrence of an adverse event will be deemed ¿probably¿ related to the study protocol if it occurs during the experimental Variable Ventilation phase or within one hour from a change in ventilator mode (the "relevant study time frames"). Additionally, ¿probable¿ attribution will be used if the event is felt to be a result of blood drawing during the study protocol. Otherwise, adverse events will be classified as unlikely related to the study pending review by the Safety Committee. Serious Adverse Events

We will adhere to the BUMC definition of 'serious adverse event' as defined as any event that results in death, is life-threatening, prolongs hospitalization, results in persistent disability, or may jeopardize the subject's health and may require medical or surgical intervention. However, as applies specifically to this study, we additionally define the following events as constituting a 'serious adverse event' related to the study if they occur during the "relevant study time frame" : 1) hemodynamic instability requiring addition of a new vasopressor or greater than 100% (doubling) increase in vasopressor dose, 2) self-extubation, 3) decrease in oxygen saturation by more than 8% or to less than 88% for more than 5 minutes, 4) pneumothorax, 5) myocardial infarction, 6) stroke, 7) death. If any 'serious adverse event', excluding death, occurs in three or more subjects during the relevant study time frame, then we feel that this is a priori greater than a chance occurrence and the study will be suspended pending further review by the Safety Committee. If one death occurs during the "relevant study time frame", then this will also lead to automatic study suspension pending review by the safety committee.

Data Reporting Plan

In the event of any SAE occurring at any time during the 6 hour window of the study intervention, the participant will be taken off the study , returned to their previous ventilator settings, and the primary care team and a study physician will be notified immediately. Follow-up and non-invasive safety data collection will continue for 24 hours. The PI will be notified asap and within 3 hours of any SAE. The independent Safety Committee will be

informed about the event within 24 hours. No further participants will be enrolled until the independent Safety Committee have assessed event in relation to possible causality of the individual event, as well as frequency (of all SAEs). If the event is determined to be unexpected and related to study procedures or intervention it will be reported to the IRB ASAP and within within 2 days of learning of the event and to the FDA ASAP and within 10 days of learning of the event (per 21 CFR 803.20 (b)(i)). If the event could reasonably suggest that the study caused or contributed to serious injury or death it will be reported to the FDA as soon as possible and within 10 working days of learning of the event. Non-serious AEs will be assessed by the independent monitors after each participant to assess if there are frequencies of non-serious AEs that are higher than what we would expect in this population. These are submitted to the IRB at the progress report.

We will implement three additional safeguards. First, because Acute Lung Injury (ALI) is less severe than ARDS, the first four subjects enrolled with have ALI, rather than the more severe ARDS. This will expose a lower risk subject group intially to this novel ventilator mode. Second, the Safety Committee will receive each subjects' completed case-report forms ASAP and within 24 -72 hours of protocol completion and will convene after each patient has completed the study protocol to provide independent review for AEs, SAEs, and UPs for individual subjects, as well as the study in aggregate, and to approve continuation of the study. Third, a progress report will be submitted to the IRB after the enrollment of the first 8 subjects, or before the one year expiration date, whichever comes first.

Summary of Safety Measures -Enroll first 4 subjects with less severe ALI -Enrollment of one subject at a time -Three hour exposure to investigational device -Real-time continuous monitoring of subject by clinically trained professional staff in addition of primary ICU team -Frequent review by independent, expert Safety committee of safety data for individual subjects and the study as a whole -Clearly defined event reporting rules -Clearly defined stopping rules.

Is there a Data Safety Monitoring Board (DSMB)? No

Section I: Potential Benefits

Describe potential benefits to be gained by the individual subject as a result of participating in the planned work.
There are no potential benefits to individual subjects for participating in this Phase I research.

Describe potential benefit(s) to society and scientific/medical knowledge of the planned work.
The potential benefit to society is the possibility of a new ventilator mode that improves important clinical outcomes, such as mortality, in a prevalent and highly morbid and mortal disease.

Discuss the risk-to-benefit ratio. Describe how benefits outweigh potential risks.
Given the results of prior pre-clinical and clinical studies of variable ventilation (attached to section S), we do not anticipate increased risk above that associated with routine critical care and mechanical ventilation. Due to the nature of ARDS, patients are decisionally imapired, and clinical research on this disease cannot be undertaken without the use of surrogate consent. We will be clear that participation in the study is completely voluntary and without potential benefit for individual subjects. We have instituted a number of measures in an attempt to maximally decrease risk in this study (please see Data Safety Monitoring Plan). Briefly, we will only enroll one patient at a time and we will expose patients for a limited amount of time to the novel ventilator mode (three hours). Additionally, the protocol will be performed with continuous clinician presence in a highly monitored ICU setting under close safety review by independent monitors. A novel mode of mechanical ventilation with the potential to decrease mortality from ARDS/ALI (currently 30-40% mortality with our current standard of care) would be of great benefit to society.

Section J: Recruitment/Consent Procedures

J1. Recruitment Procedures

Who will recruit subjects for this study?
PI's staff

Describe in detail how the research population will be identified and your methods for contacting potential subjects.
A research subject will be referred from the primary care team if they meet entry criteria. A Legally Authorized Representative (next of kin) will then be contacted to discuss the trial and to arrange a time to review the consent forms.

J2. Consent Procedures

Describe in detail who will obtain consent and describe the informed consent process. How long will subjects have to consider participating? Is consent required prior to eligibility screening? If children are enrolled, describe the assent process.

The primary person responsible for obtaining consent will be a study coordinator/respiratory therapist. A study physician will also be available at all times for any consent-related questions. The subjects' LAR can consider participating until the subject no longer meets eligibility criteria. Consent is not required prior to eligibility screening, which will be performed with a HIPPA preparatory to research. No protected health information will be recorded with identifiers during eligibility screening.

J3. Waiver of Documentation of the Informed Consent Process

Will this research include an informed consent process, but require a waiver of the requirement for documentation of consent? No

J4. Waiver of Informed Consent

Will this research require a Waiver of Informed Consent? No

Section K: Confidentiality

K1. Confidentiality

Will research data include elements which will allow the subjects to be identified? Yes

Where will research data be kept? How will such data be secured? How long will it be kept? How and when will it be destroyed?

The only research data element that will allow a subject to be identified is the medical record number. This will be linked to a subjects' study number and data through a data key which will be kept separate from the study data. This key will be locked in the primary investigator's office. Subjects will be assigned a study number and all data will be entered into the study database according to this number. Data may be stored on portable hard drives and computers; these will be password-protected. Data will be kept for five years after completion of the manuscript. It will then be destroyed by deletion from computer files and /or shredding.

Who, besides the PI, the study staff, the IRB and the sponsor, will have access to identifiable research data?

No one

State what steps will be taken to maintain confidentiality of data and privacy (or anonymity) of subjects.

The only research data element that will allow a subject to be identified is the medical record number. This will be linked to a subjects' study number and data through a data key which will be kept separate from the study data. This key will be locked in the primary investigator's office. Subjects will be assigned a study number and all data will be entered into the study database according to this number. Data may be stored on portable hard drives and computers; these will be password-protected. Data will be kept for five years after completion of the manuscript. It will then be destroyed by deletion from computer files and /or shredding.

Will you obtain a Certificate of Confidentiality for this study? No

K2. HIPAA Compliance

Research is exempt from the Privacy Rule if there will be no collection of protected health information and/or the PI is not a member of a HIPAA covered workforce. Is this research subject to the HIPAA Privacy Rule? Yes

HIPAA Forms:

Authorization Form
Preparatory to Research

Section L: Cost/Payment

What costs / potential costs will subjects incur (include travel, parking, medication, etc.)? How will the cost of research visits / procedures be covered? Will the subject (or the subject’s insurance) be responsible for any research related costs? If yes, state specifically which items the subject (or the subject’s insurance) will be responsible for and the cost of each.

No costs to the subject. Extra laboratory testing done as part of the study will be paid for by the study grant.

If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc.) of the payment. Describe any other reimbursement that will be provided to subjects, (i.e. travel, parking, public transportation, etc.). Explain specifically how and when these reimbursements for expenses will be paid. Specify your plan for reimbursement if a subject withdraws from the study.

n/a

Section M: Genetics

How would you classify your genetic study?

Discuss the potential for psychological, social, and/or physical harm subsequent to participation in this research. Please discuss, considering the following areas: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.

Will subjects be provided with genetic results? Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling and under what conditions will it be provided? If there is the possibility that a family's pedigree will be presented or published, please describe how you will protect family members' confidentiality?

Section N: Biological Sample Collection

Sample: Blood

What is the purpose of the sample collection?

Arterial blood sample will be taken for analysis for arterial blood gas measurements (pH, PaO2, PaCO2, HCO3, saturation) and to determine if levels of plama markers of lung injury (cytokines IL-6, IL 1receptor antagonist, sTNFreceptor I, and surfactant protein D) are different between the two ventilator modes being studied.

For blood draws, specify the amount drawn at each visit and across the course of the subject's entire participation time.

Three blood samples will be obtained in total during the six hour study period. One arterial blood sample of will be taken at study onset, one at three hours, and one at six hours. Each sample will be 3ml in size, for a total of 9ml of blood drawn over six hours. Some patients enrolled in this trial will have had arterial catheters placed by the primary team, allowing noninvasive blood drawing for most subjects. Others will require separate arterial blood gas drawing.

Is there the possibility that cell lines will be developed with this sample? No

Sample will be obtained from:

Directly From Subject

Will the sample be stripped of identifiers? Yes

<u>If sample will be released outside BU/BUMC:</u>

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified? If coded, who will hold the code? How will it be secured? When/how will it be destroyed? N/A

Will sample material be sold or transferred to any third parties? If so, describe the recipient. Will the information be de-identified? If so, describe how.

N/A

<u>If sample will be banked for future use:</u>

Where will the sample be banked and for how long? Will the subject be re-consented for future use?

N/A

Does the banking institution have an IRB approved policy for the distribution of samples?
N/A

If the entire sample will NOT be used during the course of this research study:

Will the remaining sample be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?
Yes. Any plasma not used during the study will be discarded after all testing has been completed.

Will samples be made available to the research subject (or his/her medical doctor) for other testing? No

If a subject withdraws from the study:

Will the subject have the option to get the remaining portion of his/her sample back? No

Will the remaining sample be discarded? If not, will it be kept anonymously? What will happen to the sample if the subject revokes authorization?
If a subject withdraws from the study, his or her sample will be discarded.

Will data obtained from the sample be deleted? What will happen to the data if the subject revokes authorization?
If a subject withdraws, data already obtained from that subject will not be deleted; however, no further data will be collected and no further blood tests will be run.

Will study data or test results be recorded in the subject's medical records? Yes

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?
The only tests done for research purposes that have any established clinical value are the arterial blood gas measurements, i.e. Ph, pCO2, and pO2. Therefore, we will make sure that these results are revealed to the subject's doctor and included in the medical record. Other research data to be collected have no established medical value and will not be revealed to the subject or subject's doctor.

Please identify all third parties, including the subject's physician, to receive the test results.
The subject's physician will receive arterial blood gas results.

Section O. Drug or Biological Agents

Does this study involve administering drugs or biological agents? No

If an IND Number is required, either enter the number, or the word "pending" if the number has not yet been assigned. Protocols requiring an IND Number will not be approved until the number is provided.

IND Number:

Responsibile for storage and documentation of drugs / biological agents:

In the text box below state the name of the drug / biological agent, the name of the manufacturer and who is holding the IND.

Does this research involve a NEW use of an approved drug? If yes, the drug/biological agent name, the name of the manufacturer, and who is holding the IND.

FDA approved drugs being used in accordance with FDA labeling which will be administered as part of this research study:

Section P. Device Studies

Categorize the device:

Experimental device

If applicable, provide the IDE number / HDE number. State the name of the device, the manufacturer and who holds the IDE.

An FDA IDE application has been submitted and is currently under review. No study procedure will begin until FDA IDE is recieved.

Does this study involve the use of an investigational electrical device? Yes

If you believe this study involves an NSR (non-significant risk) device, please justify this determination.

Section Q. Consent Form(s)

Variable Ventilation Study

Section R: Recruitment Materials

Mode: Flyer

Exact language of recruitment material:

Do You Have a Patient with the Following?

Acute respiratory decline Bilateral infiltrates on a chest x-ray PaO2 / FiO2 less than 300 No CHF

If so, your patient may have Acute Lung Injury (ALI) or the Acute Respiratory Distress Syndrome (ARDS)?

Page XXXX to screen your patient for the Variable Ventilation Study

(Flyer to be posted in the Boston Medical Center intensive care units)

Special Routing

Biomedical Engineering

NAME AND ADDRESS OF SPONSOR

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Pulmonary, Critical Care and Allergy Medicine

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REPORTS OF PRIOR INVESTIGATIONS

Pre-Clinical Variable Ventilation Studies

In multiple pre-clinical experiments, cultured Type II pneumocytes show significantly increased release of surfactant and less cellular injury when exposed to variable stretch as compared with monotonous stretch.[1] Surfactant is typically depleted in ALI/ARDS, resulting in decreased lung compliance and increased risk of barotrauma. In vivo studies using normal guinea pigs confirmed that variable ventilation (VV) increased surfactant secretion, improved lung mechanics, and decreased biomarkers of lung injury compared with conventional ventilation at the same mean tidal volume.[2] Further studies with animal models of ARDS in multiple laboratories have confirmed these findings: variable ventilation has resulted in improved oxygenation, compliance, and alveolar recruitment while decreasing histological and biomarker evidence of lung injury in rodent,[3, 4] porcine,[5, 6, 7, 8, 9] and sheep[10] models of ARDS when compared with conventional, ARDS Net-type strategies. One animal study[11] by Nam et al using a much larger variability (up to 230%) than the degree of variability we plan to investigate (40%) failed to confirm these findings (see also page 11, item 8). Interestingly, the large level of variability studied by Nam et al would not be expected to improve lung function according to Suki's mathematical models.[12] The 40% variability we propose to study was predicted to be the optimal "tuned noise" in mathematical models, [12] which was later validated in an animal model of lung injury.[6]

The following list contains more detailed summaries of the above cited studies that involve the application of respiratory variability to improve lung function. The first five studies originated from Professor Suki's laboratory; Dr. Suki's method of applying variable ventilation is the method that will be incorporated into our ventilator system. The other listed studies also involved variable ventilation, but originated from other laboratories using different patterns of variability.

1. Arold SP, Suki EB, Suki B. Variable stretch pattern enhances surfactant secretion in alveolar type II cells in culture. Am J Physiol Lung Cell Mol Physiol (January 9, 2009) doi:10.1152/ajplung.90454.2008. [1] Secretion of pulmonary surfactant, which maintains low surface tension within the lung, is primarily mediated by mechanical stretching of alveolar epithelial type II (AEII) cells. We have shown that guinea pigs ventilated with random variations in frequency and tidal volume had significantly larger pools of surfactant in the lung than animals ventilated in a monotonous manner. Here we test the hypothesis that variable stretch patterns imparted on the AEII cells result in enhanced surfactant secretion. AEII cells isolated from rat lungs were exposed to equi-biaxial strains of 12.5%, 25%, or 50% change in surface area (ΔSA) at 3 cycles/min for 15, 30, or 60 min. [3H]-labeled phosphatidylcholine (PC) release and cell viability were measured 60 min following the onset of stretch. While secretion increased following 15 min stretch at 50% ΔSA and 30 min stretch at 12.5% ΔSA, 60 min of cyclic stretch

diminished surfactant secretion regardless of strain. When cells were stretched using a variable strain profile in which the amplitude of each stretch was randomly pulled from a uniform distribution, surfactant secretion was enhanced both at 25% and 50% mean ΔSA with no additional cell injury. Furthermore, at 50% mean ΔSA, there was an optimum level of variability that maximized secretion, implying that mechanotransduction in these cells exhibits a phenomenon similar to stochastic resonance. These results suggest that application of variable stretch may enhance surfactant secretion, possibly reducing the risk of ventilator-induced lung injury. Variable stretch-induced mechanotransduction may also have implications for other areas of mechanobiology.

2. Arold SP, Suki B, Alencar AM, et al. Variable ventilation induces exogenous surfactant release in normal guinea pigs. Am J Physiol Lung Cell Mol Physiol 2003; 285: L370-L375.[2] Variable or noisy ventilation, which includes random breath-to-breath variations in tidal volume (VT) and frequency, has been shown to consistently improve blood oxygenation during mechanical ventilation in various models of acute lung injury. To further understand the effects of variable ventilation on lung physiology and biology, we mechanically ventilated 11 normal guinea pigs for 3 h using constant-VT ventilation (n = 6) or variable ventilation (n = 5). After 3 h of ventilation, each animal underwent whole lung lavage to determine alveolar surfactant content and composition, while protein content was assayed as a possible marker of injury. Another group of animals underwent whole lung lavage in the absence of mechanical ventilation to serve as an unventilated control group (n = 5). Although lung mechanics did not vary significantly between groups, we found that variable ventilation improved oxygenation, increased surfactant levels nearly twofold, and attenuated alveolar protein content compared with animals ventilated with constant VT. These data demonstrate that random variations in VT promote endogenous release of biochemically intact surfactant, which improves alveolar stability, apparently reducing lung injury.

3. Arold SP, Mora R, Lutchens KR et al. Variable tidal volume ventilation improves lung mechanics and gas exchange in a rodent model of acute lung injury. Am J Resp Crit Care Med 2002; 165: 366-71.[3] Random variations in breath rate and tidal volume during mechanical ventilation in the setting of acute lung injury have been shown to improve arterial oxygen tension. To test whether this improvement occurs over a specific range of variability, we examined several ventilation protocols in guinea pigs with endotoxin-induced lung injury. In Group I (n = 10), after 30 min of conventional volume-cycled ventilation, animals were ventilated with variable ventilation for 30-min intervals, during which time tidal volume was randomly varied by 10, 20, 40, and 60% of the mean, while simultaneously adjusting the frequency to maintain constant minute ventilation. In a second group of animals (Group II, n = 4), conventional volume-cycled ventilation was administered for 3 h. Variable ventilation significantly improved lung function over conventional volume-cycled ventilation. In Group I, lung elastance decreased and blood

oxygenation increased significantly during periods of 40 and 60% variable ventilation ($p < 0.05$), compared with conventional ventilation. These data indicate that variable ventilation is effective in improving lung function and gas exchange during acute lung injury.

4. Thammanomai A, Hueser LE, Majumdar A, Bartola K, Suki E, Suki B. Design of a new variable-ventilation method optimized for lung recruitment in mice. J Appl Physiol 104: 1329–1340, 2008. First published March 13, 2008; doi:10.1152/japplphysiol.01002.2007.[4] Variable ventilation (VV), characterized by breath-to-breath variation of tidal volume (VT) and breathing rate (f), has been shown to improve lung mechanics and blood oxygenation during acute lung injury in many species compared with conventional ventilation (CV), characterized by constant VT and f. During CV as well as VV, the lungs of mice tend to collapse over time; therefore, the goal of this study was to develop a new VV mode (VVN) with an optimized distribution of VT to maximize recruitment. Groups of normal and HCl-injured mice were subjected to 1 h of CV, original VV (VVO), CV with periodic large breaths (CVLB), and VVN, and the effects of ventilation modes on respiratory mechanics, airway pressure, blood oxygenation, and IL-1 were assessed. During CV and VVO, normal and injured mice showed regional lung collapse with increased airway pressures and poor oxygenation. CVLB and VVN resulted in a stable dynamic equilibrium with significantly improved respiratory mechanics and oxygenation. Nevertheless, VVN provided a consistently better physiological response. In injured mice, VVO and VVN, but not CVLB, were able to reduce the IL-1-related inflammatory response compared with CV. In conclusion, our results suggest that application of higher VT values than the single VT currently used in clinical situations helps stabilize lung function. In addition, variable stretch patterns delivered to the lung by VV can reduce the progression of lung injury due to ventilation in injured mice.

5.Bellardine CL, Hoffman AM, Tsai L, et al. Comparison of variable and conventional ventilation in a sheep saline lavage lung injury model. Crit Care Med 2006; 34(2): 439-445.[10] Objective: There has recently been considerable interest in alternative lung-protective ventilation strategies such as variable ventilation (VV). We aimed at testing VV in a large animal lung injury model and exploring the mechanism of improvement in gas exchange seen with VV. Design: Randomized, controlled comparative ventilation study. Setting: Research laboratory at a veterinary hospital. Subjects: Female sheep weighing 59.8 ±10.57 kg and excised calf lungs. Interventions: In a sheep saline lavage model of lung injury, we applied VV, whereby tidal volume (VT) and frequency (f) varied on each breath. Sheep were randomized into one of two groups (VV, n = 7; or control, n = 6) and ventilated for 4 hrs with all mean ventilation settings matched. Measurements and Main Results: Gas exchange, lung mechanics, and hemodynamic measures were recorded over the 4 hrs. VV sheep showed improvement in gas exchange (i.e., oxygenation and carbon dioxide elimination) and ventilation pressures (i.e., reduced mean and peak

airway pressures), but control sheep did not. VV sheep also displayed lower-lung elastance and mechanical heterogeneity in comparison with control sheep from 2 to 4 hrs of ventilation. To study the mechanism behind improvements seen with VV, we examined the time course associated with the enhanced recruitment occurring during VV in eight saline-lavaged excised calf lungs. We found that the recruitment associated with a larger VT during VV lasted over 200 secs, nearly an order of magnitude greater than the average time interval between large VT deliveries during VV. Conclusions: The application of VV in a large animal model of lung injury results in improved gas exchange and superior lung mechanics in comparison with CV that can be explained at least partially by the long-lasting effects of the recruitments occurring during VV.

6. W. Alan Mutch, MD; Stefan Harms, MD; Gerald R. Lefevre, MD; M. Ruth Graham, MD; Linda G. Girling, BSc; Stephen E. Kowalski, MD. Biologically variable ventilation increases arterial oxygenation over that seen with positive end-expiratory pressure alone in a porcine model of acute respiratory distress syndrome. Crit Care Med 2000; 28:2457–2464.[6] Objectives: We compared biologically variable ventilation (BVV) with conventional control mode ventilation (CV) in a model of acute respiratory distress syndrome (ARDS) at 10 cm H2O positive end-expiratory pressure. Design: Randomized, controlled, prospective study. Setting: University research laboratory. Subjects: Farm-raised 3- to 4-month-old swine. Interventions: Oleic acid (OA) was infused at 0.2 mL/kg/hr with an FIO2 of 0.5 and 5 cm H2O positive end-expiratory pressure until PaO2 was <60 mm Hg; then all animals were placed on an additional 5 cm H2O positive end-expiratory pressure for the next 4 hrs. Animals were assigned randomly to continue CV (n = 9) or to have CV computer controlled to deliver BVV (variable respiratory rate and tidal volume; n = 8). Hemodynamic, expired gas, airway pressure, and volume data were obtained at baseline (before OA), immediately after OA, and then at 60-min intervals for 4 hrs. Measurements and Main Results: At 4 hrs after OA injury, significantly higher PaO2 (213 ± 17 vs. 123 ± 47 mm Hg; mean 6 SD), lower shunt fraction (6% ± 1% vs. 18% ± 14%), and lower PaCO2 (50 ± 8 vs. 65 ±11 mm Hg) were seen with BVV than with CV. Respiratory system compliance was greater by experiment completion with BVV (0.37 ± 0.05 vs. 0.31 ± 0.08 mL/cm H2O/kg). The improvements in oxygenation, CO2 elimination, and respiratory mechanics occurred without a significant increase in either mean airway pressure (14.3 ± 0.9 vs. 14.9 ± 1.1 cm H2O) or mean peak airway pressure (39.3 ± 3.5 vs. 44.5 ± 7.2 cm H2O) with BVV. The oxygen index increased five-fold with OA injury and decreased to significantly lower levels over time with BVV. Conclusions: In this model of ARDS, BVV with 10 cm H2O positive end-expiratory pressure improved arterial oxygenation over and above that seen with CV with positive end-expiratory pressure alone. Proposed mechanisms for BVV efficacy are discussed.

7. Peter M. Spieth, Alysson R. Carvalho, Paolo Pelosi, Catharina Hoehn, Christoph Meissner , Michael Kasper, Matthias Hübler, Matthias von Neindorff, Constanze Dassow, Martina Barrenschee, Stefan Uhlig, Thea Koch, Marcelo Gama de Abreu. Variable tidal volumes improve lung protective ventilation strategies in experimental lung injury. Am J Respir Crit Care Med. 2009; 179(8):684-93.[9] Rationale: Noisy ventilation with variable tidal volumes may improve respiratory function in acute lung injury. Objectives: To determine the impact of noisy ventilation on respiratory function and its biological effects on lung parenchyma compared to conventional protective mechanical ventilation strategies. Methods: In a porcine surfactant-depletion model of lung injury, we randomly combined noisy ventilation with either the ARDS Network protocol or the open lung approach (n = 9 per group). Measurements and Main Results: Respiratory mechanics, gas exchange, and distribution of pulmonary blood flow were measured at intervals during 6h. Post-mortem, lung tissue was analyzed to determine histological damage, mechanical stress, and inflammation. We found that, at comparable minute ventilation, noisy ventilation: (1) improved arterial oxygenation and reduced mean inspiratory peak airway pressure as well as elastance of the respiratory system compared to the ARDS Network protocol and the open lung approach; (2) redistributed pulmonary blood flow to caudal zones compared to the ARDS Network protocol and to peripheral ones compared to the open lung approach; (3) reduced histological damage in comparison to both protective ventilation strategies; (4) did not increase lung inflammation or mechanical stress. Conclusions: Noisy ventilation with variable tidal volumes and fixed respiratory frequency improves respiratory function and reduces histological damage compared to standard protective ventilation strategies.

8. Arthur J. Nam, Roy G. Brower, Henry E. Fessler, and Brett A. Simon. Biologic variability in mechanical ventilation rate and tidal volume does not improve oxygenation or lung mechanics in canine oleic acid lung injury. Am J Respir Crit Care Med Vol 161. pp 1797–1804, 2000.[11] Mechanical ventilation in patients with acute respiratory distress syndrome and acute lung injury (ALI) remains a difficult challenge because of the conflict between maintaining adequate gas exchange and furthering lung injury via overdistention. In a recent study, Lefevre and colleagues (Am J Respir Crit Care Med 1996; 154:1567–1572) suggested that mechanical ventilation with natural biologic variability (BV) in breath-to-breath respiratory frequency (f) and VT could reduce lung injury and improve gas exchange without increases in mean airway pressure (Paw) or peak inspiratory pressure (PIP). However, significant differences in cardiac output (CO), PaCO2, pH, and delivered VT between the treatment groups in their study could have influenced these results. Because of the potential implications of these findings for patient care, we attempted to confirm these findings by Lefevre and colleagues in a canine model of oleic acid-induced lung injury. Eighteen mongrel dogs were anesthetized in the supine position, paralyzed, and mechanically ventilated with 50% O2 at f 15 breaths/min, and VT was adjusted to achieve an end-tidal CO2 of 30 to 35 mm Hg. Lung injury was produced

by infusion of 0.06 ml/kg oleic acid solution into the right atrium over a 30-min period. Animals were then randomized to either conventional ventilation at the baseline settings (n = 9) or to BV at the same mean VT and f (n = 9). Both groups received comparable degrees of injury, and hemodynamic and ventilatory parameters were closely matched, with no differences in mean VT, PIP, mean Paw, PaCO2, pH, CO, pulmonary artery occlusion pressure, or arterial pressure (Pa). However, no differences between the two groups were found in PaO2, shunt, or static compliance over a 4-h period. When hemodynamic and ventilatory parameters were well matched in a canine model of ALI, BV showed no advantage over conventional ventilation at constant VT and f.

Variable Ventilation Studies in Humans

Recently, a published study of patients undergoing abdominal aortic aneurysmectomy, as well as pilot studies of variable ventilation in humans by Professor Gattinoni's group in Italy and Professor Mutch's group in Canada have shown that delivering variable breaths to humans through a mechanical ventilator is safe and appears effective in providing short-term improvements in oxygenation and lung mechanics. Abstracted summaries of the three human studies published to date appear below.

1. Boker A, Haberman CJ, Girling L et al. Variable ventilation improves perioperative lung function in patients undergoing abdominal aortic aneurysmectomy. Anesthesiology 2004; 100(3): 608-16. [13] Background: Optimizing perioperative mechanical ventilation remains a significant clinical challenge. Experimental models indicate that "noisy" or variable ventilation (VV)—return of physiologic variability to respiratory rate and tidal volume—improves lung function compared with monotonous control mode ventilation (CV). VV was compared with CV in patients undergoing abdominal aortic aneurysmectomy, a patient group known to be at risk of deteriorating lung function perioperatively. Methods: After baseline measurements under general anesthesia (CV with a tidal volume of 10 ml/kg and a respiratory rate of 10 breaths/min), patients were randomized to continue CV or switched to VV (computer control of the ventilator at the same minute ventilation but with 376 combinations of respiratory rate and tidal volume). Lung function was measured hourly for the next 6 h during surgery and recovery. Results: Forty-one patients for aneurysmectomy were studied. The characteristics of the patients in the two groups were similar. Repeated-measures analysis of variance (group-time interaction) revealed greater arterial oxygen partial pressure (P = 0.011), lower arterial carbon dioxide partial pressure (P = 0.012), lower dead space ventilation (P = 0.011), increased compliance (P = 0.049), and lower mean peak inspiratory pressure (P = 0.013) with VV. Conclusions: The VV mode of ventilation significantly improved lung function over CV in patients undergoing abdominal aortic aneurysmectomy.

2. Taccone P, Polli F, Ciumello V et al. Effects of variable ventilation during lung protective mechanical ventilation strategy in ALI/ARDS patients. Presented at the American Thoracic Society International Conference, 2008.[14] Background: Variable ventilation (VV) has been recently described as a new ventilatory modality mimicking the spontaneous variability in physiologic breathing pattern. The hemodynamic and respiratory effects of VV were never evaluated during low tidal volume ventilation in ALI/ARDS patients. Methods: We studied 6 ALI/ARDS patients ventilated according to the NIH protocol (60±17 yrs, 4M/2F, PaO2/FiO2 161±4 with PEEP 11±1cm H2O, Vt 6-8ml/kg). Using a Servo 300 ventilator connected to a personal computer, we delivered VV, (i.e., a random sequence of Vt from a uniform probability falling between ± 0%, ± 20%, ± 40%, ± 60%) of the mean Vt. Each level of variability was applied for one hour, measuring continuously hemodynamic and respiratory parameters. Gas exchanges and EELV with helium dilution technique were assessed at the end of each period. Moreover, the potential of lung recruitment was assessed by CT analysis. Results: VV was well tolerated in every patient. Increasing variability was associated with an increase in EELV and improvement in oxygenation, while CO2 exchanged remained unchanged. Patients' response was associated to lung recruitability.

3. B. G. McCarthy, MD, M. McMullen, MD, L. Docking, MD, Z. Bshouty, MD, L. G. Girling, BSc Hon and S. E. Kowalski. A pilot study of biologically variable ventilation in ALI/ARDS: Trends towards an improved ventilatory strategy. Medical University of Manitoba, Winnipeg, MB, Canada. Presented at ATS 2009, San Diego, CA.[15] Introduction: The currently accepted standard of care for patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) includes low tidal volume ventilation per the ARDS Net protocol. An optional mode of ventilation is biologically variable ventilation (BVV). With BVV, the ventilator varies Vt, but at a fixed minute ventilation. Thus, BVV introduces a noisy, more physiologic breathing signal. We hypothesized that BVV would improve respiratory mechanics and gas exchange in human subjects with ALI/ARDS. Methods: A crossover trial was undertaken with patients receiving 4 hours of ARDS Net protocol with CMV and 4 hours of BVV. Patients were randomized to begin with either CMV or BVV. With BVV, the mean Vt was 8ml/kg. After 4 hours the patients were switched to the other mode of ventilation. At hourly intervals the following were measured: ABG, Vd/Vt, compliance, and peak and plateau respiratory pressures. Statistical analysis included repeated measures ANOVA. Results: Nine patients were evaluated in total with varying etiologies of ALI/ARDS. No deaths were attributed to the ventilatory strategy itself. At 4 hours, BVV as compared to CMV was associated with a trend towards improved ventilation as the PaCO2 decreased from 56.3 to 51.3 mmHg (p=0.085) and Vd/Vt decreased from 0.68 to 0.64(p=0.017). Compliance increased from 35 to 38 ml/cmH2O (p=0.049). A trend towards improved oxygenation with BVV was observed as the Pa02 at 4 hours was noted to be 124 mmHg in the BVV group and 97 mmHg in the CMV group (p=0.21). The oxygenation index at 4 hours was 9.9 and 7.1 cmH2O/mmHg in the CMV and BVV

groups, respectively (p=0.13). Conclusion: In patients with ALI/ARDS we have shown that BVV as compared to CMV using the ARDS Net protocol is a safe and potentially improved mode of ventilation. BVV warrants further examination in order to validate and quantify the improvements suggested by this study

The form of variable ventilation designed by Mutch and colleagues was derived from the respiratory patterns of a spontaneously breathing dog. In these human studies, variable ventilation was shown to be safe and effective in improving oxygenation in normal patients undergoing vascular surgery. Preliminary unpublished data by Suki's group have shown that the form of variable ventilation we intend to study ─ derived from Suki's mathematical modeling of optimal "noise" delivered to nonlinear pressure-volume relationships of the injured lung ─ provided superior recruitment and oxygenation, compared with the Mutch technique.

In summary, current data demonstrate that variable ventilation decreases lung injury and improves lung function when compared with conventional low-tidal-volume (ARDS Net) ventilation. The mechanisms behind the lung-protective nature of variable ventilation involve the ability to ventilate the lung at lower and less injurious mean pressures while achieving increased recruitment of collapsed alveoli. This finding is likely secondary to the non-linear pressure-volume relationships of the lung, as well as enhanced surfactant output seen in animal studies of variable ventilation. Because of this potential for an effective, less-injurious mode of mechanical ventilation, we propose the first in-human studies of the Suki mode of variable ventilation in patients with ALI or ARDS.

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15. McCarthy BG, McMullen M, Docking et al. A pilot study of biologically variable ventilation in ALI/ARDS: Trends towards an improved ventilatory strategy. Medical University of Manitoba, Winnipeg, MB, Canada. Presented at ATS 2009, San Diego, CA.

INVESTIGATIONAL PLAN

This is a Phase I study of a novel method of mechanical ventilation called Variable Ventilation. This method of ventilation is provided through the Puritan-Bennett 840, a standard mechanical ventilator used in the Boston Medical Center critical care areas. This ventilator has been modified to run a program via laptop computer that randomly varies tidal volume and respiratory rate. This modified ventilator will be studied with an FDA Investigational Device Exemption and labeled as experimental use only. The ventilator will retain all functionality of its unmodified version, plus the ability to run the custom variable ventilation program.

PURPOSE

In order to study the safety, tolerability, and preliminary efficacy (Objectives 1 to 4 and Hypotheses 1 to 4, see below) of variable ventilation in human subjects with ALI/ARDS, we plan to perform a Phase I, randomized cross-over design trial to study the Variable Ventilation Mode developed by Professor Bela Suki at Boston University.

Objective 1: To determine whether variable ventilation (VV) is safe and well-tolerated in patients with acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS).

Hypothesis 1: VV is safe and well-tolerated in ALI and ARDS.

Objective 2: To determine whether VV improves gas exchange in patients with ALI and ARDS.

Hypothesis 2: VV results in significant improvements in PaO2 versus conventional ARDS Net lung protective ventilation.

Objective 3: To determine whether VV improves lung mechanics in patients with ALI and ARDS.

Hypothesis 3: VV results in improved lung compliance, lowered mean airway pressure, and decreased dead space versus ARDS Net ventilation.

Objective 4: To determine whether VV results in changes in serum biomarkers associated with ventilator-associated lung injury.

Hypothesis 4: VV results in reduced circulating levels of IL-6, IL-8, IL-1 receptor antagonist, soluble TNF-α receptor I and surfactant protein-D compared with ARDS Net ventilation.

We have determined that on average 10 patients with ALI/ARDS are admitted every month to our ICUs. Speculating that one-half of these patients meet entry criteria, and 20% of these consent for the trial, we anticipate enrolling an average of one patient monthly. Therefore, enrollment should last 16 months.

PROTOCOL

Inclusion and Exclusion Criteria

This study will include adult patients meeting the American-European Consensus definition of ALI or ARDS,[21] defined as acute onset, PaO2/FiO2 ratio <300 (ALI) and <200 (ARDS), (if arterial blood gas data is unavailable, SaO2/FiO2 ratio < 315 for ALI or < 235 for ARDS will be utilized[22]), bilateral radiographic infiltrates, and no suspicion of left atrial hypertension. Additional inclusion criteria are age > 18 years, placement on mechanical ventilation using a volume or pressure-controlled mode, and admission to Boston Medical Center Surgical, Medical, or Coronary Intensive Care Unit (Table 1).

Potential subjects will be excluded from the study if:

- There is a "Do not resuscitate" order.
- There is suspicion of increased intracranial pressure.
- The patient is pregnant (urine pregnancy test for all women of child-bearing age).
- There is a scheduled transport out of ICU during the study protocol.
- There is coagulopathy (INR > 2.0 or PTT > 50) or severe thrombocytopenia (platelets < 20,000).
- The patient has ARDS or ALI criteria for greater than 7 days prior to enrollment.
- The primary care team does not assent to the study.

See Table 2 for a complete list of exclusion criteria. Eligible patients will be identified by the primary intensive care unit team, who will notify the study coordinator. After consent is obtained from the potential subject's legally authorized representative, the subject will begin the study protocol only when a set of clinical stability criteria are met (see Table 3). These clinical stability criteria include:

1. Hemodynamic stability, defined as mean arterial pressure greater than 60mm Hg and heart rate greater than 50 and less than 130 beats/minute.

Table 1. Study inclusion criteria.

--Age ≥ 18 years.

--Patient requires mechanical ventilation (either volume-controlled or pressure-controlled mode) for fewer than 14 days.

--Admitted to medical, surgical, or coronary intensive care unit at Boston Medical Center.

--Meets American-European Consensus criteria for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).

a. Acute onset of respiratory compromise AND

b. Bilateral front chest radiographic infiltrates AND

c. PaO2/FiO2 ratio less than 300 for ALI or less than 200 for ARDS (or SpO2/FiO2 ratio less than 315 for ALI or less than 235) AND

d. No clinical signs of left atrial hypertension OR a known pulmonary wedge pressure less than 18 mm Hg.

--Primary care team assents to enrollment in this study.

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2. Respiratory stability, defined as a respiratory rate less than 35 breaths/minute, O_2 saturation greater than 88%, peak pressure on ventilator less than 40 cm H_20, suctioning required less than once hourly.
3. Acid-base stability, defined as a pH between 7.2 and 7.55.
4. Neurological stability, defined as lack of agitation by Ramsay Sedation Score greater than or equal to 2.

Procedures

A randomized envelope will be opened to reveal the order of ventilation strategies: either variable ventilation (VV) followed by conventional ARDS Net ventilation (CV), or conventional ARDS Net ventilation (CV) followed by variable ventilation (VV).

Each patient will be ventilated for three hours on each ventilator strategy, for a total of six hours. Baseline recordings of patient demographics (e.g., age, sex, race, location of care) and details of severity of illness (e.g., APACHE II, lung injury Score, diagnosis, reason for mechanical ventilation) will be recorded prior to starting the study protocol.

Conventional ventilation (CV) will involve continuing the subject's ventilator settings prior to instituting the protocol. These will fall into the range of 6 to 8cc/kg predicted body weight, with PEEP and FiO2 set as per the ARDS Net protocol for lower PEEP and higher FiO2 (Table 4).

During variable ventilation, the patient's target minute volume will be set to approximate the same minute volume delivered during the patient's baseline period of ventilation. The mean tidal volume will be set to equal the tidal volume of conventional

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Table 2. Study exclusion criteria.

--Patient has a do not resuscitate order.

--Increased intracranial pressure.

--Pregnancy (women of child-bearing age will be given a urine test).

--Scheduled transport out of ICU during planned study protocol.

--Coagulopathy (INR > 2.0 or PTT > 50).

--Severe thrombocytopenia (platelets < 20,000).

--Has met ARDS or ALI criteria for more than seven days prior to enrollment.

--Primary care team does not assent to enrollment.

Table 3. Clinical Stability Criteria:

--Hemodynamic stability: mean arterial pressure greater than 60 mm Hg AND heart rate greater than 50 beats/minute and less than 130 beats/minute AND (receiving a maximum of two vasopressor medications) for at least one hour prior to the start of the protocol.

--Respiratory stability: respiratory rate less than 35 breaths/minute, AND oxygen saturation greater than 88 percent, AND peak pressure on ventilator less than 40 cm H2O, AND suctioning required less than once hourly.

--Acid-base stability: pH greater than 7.20 and less than 7.55.

--Neurological stability: absence of agitation; Ramsay Sedation Score ≥ 2.

--If loss of one or more of these clinical stability criteria are occurs during the six-hour study protocol, the protocol will be suspended.

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ventilation at baseline, but with a 40-percent variability. For example, if a subject at baseline was receiving 6 cc/kg per breath with conventional ventilation, variable ventilation will randomly deliver any tidal volume between 8.4 cc/kg and 3.6 cc/kg on a breath-by-breath basis, with an average of 6 cc/kg delivered over the course of the study period. The mean respiratory rate will be set to achieve the target minute volume.

Oxygenation and ventilation will be monitored via continuous oximetry and continuous end-tidal CO2 monitoring. If the end-tidal CO2 signal becomes unreliable, a central venous or arterial blood gas will be noninvasively drawn through an indwelling catheter (an arterial line will be the preferred site; a central venous line will be used if no arterial catheter is in place) after any change to the ventilator settings. If the continuous pulse oximetry signal is lost, efforts will be made to obtain a signal from alternate sites (finger, forehead, or ear probes). If no oximetry signal can be obtained after these efforts, then the primary team will be notified and the study will be suspended due to inability to appropriately monitor vital signs.

Except during suctioning, the FiO2 will be kept constant during the six-hour study period. Suctioning will be allowed hourly as per clinical necessity, with the FiO2 increased to 100 percent during suctioning and returned to the preceding value after suctioning is complete. Triggers for clinical necessity of suctioning will include a peak inspiratory pressure (PIP) increase of more than 10 cm H2O above baseline, development of audible rhonchi, or if sputum is visible in the ventilator circuit tubing. No study data (e.g., ABG, biomarkers, and mechanics) will be

collected during suctioning or when the FiO2 is set at 100 percent and for fifteen minutes thereafter. The frequency of suctioning

Table 4. ARDS Net protocol.

ARDSNet

NIH NHLBI ARDS Clinical Network
Mechanical Ventilation Protocol Summary
www.ardsnet.org

INCLUSION CRITERIA: Acute onset of

1. $PaO_2/FiO_2 \leq 300$ (corrected for altitude)
2. Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

PART I: VENTILATOR SETUP AND ADJUSTMENT

1. Calculate predicted body weight (PBW)
   Males = 50 + 2.3 [height (inches) - 60]
   Females = 45.5 + 2.3 [height (inches) -60]
2. Select Assist Control Mode
3. Set initial TV to 8 ml/kg PBW
4. Reduce TV by 1 ml/kg at intervals ≤ 2 hours until TV = 6ml/kg PBW.
5. Set initial rate to approximate baseline VE (not > 35 bpm).
6. Adjust TV and RR to achieve pH and plateau pressure goals below.
7. Set inspiratory flow rate above patient demand (usually > 80L/min)

OXYGENATION GOAL: PaO_2 55-80 mmHg or SpO_2 88-95%
Use incremental FiO_2/PEEP combinations below to achieve goal

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0
PEEP	14	14	14	16	18	20	22	24

PLATEAU PRESSURE GOAL: ≤ 30 cm H_2O
Check Pplat (0.5 second inspiratory pause), SpO_2, Total RR, TV and pH (if available) at least q 4h and after each change in PEEP or TV.

If Pplat > 30 cm H_2O: decrease TV by 1 ml/kg steps (minimum = 4 ml/kg).
If Pplat < 25 cm H_2O: TV < 6 ml/kg, increase TV by 1 ml/kg until Pplat > 25 cm H_2O or TV = 6 ml/kg.
If Pplat < 30 and breath stacking occurs: may increase TV in 1 ml/kg increments (maximum = 8 ml/kg).

pH GOAL: 7.30-7.45
Acidosis Management: (pH < 7.30)
If pH 7.15-7.30: Increase RR until pH > 7.30 or $PaCO_2$ < 25 (Maximum RR = 35).
If RR = 35 and $PaCO_2$ < 25, may give $NaHCO_3$.
If pH < 7.15: Increase RR to 35.
If pH remains < 7.15 and $NaHCO_3$ considered or infused, TV may be increased in 1 ml/kg steps until pH > 7.15 (Pplat target may be exceeded).
Alkalosis Management: (pH > 7.45) Decrease vent rate if possible.

Loss of any of the stability criteria including:

--Hemodynamic stability: mean arterial pressure greater than 60 mm Hg AND heart rate greater than 50 beats/minute and less than 130 beats/minute AND receiving a maximum of two vasopressor medications) for at least one hour prior to the start of the protocol.

--Respiratory stability: respiratory rate less than 35 breaths/minute, AND oxygen saturation greater than 88 percent, AND peak pressure on ventilator less than 40 cm H2O, AND suctioning required less than once hourly.

--Acid-base stability: pH greater than 7.20 and less than 7.55.

--Neurological stability: absence of agitation; Ramsay Sedation Score ≥ 2.

--Inability to monitor pulse oximetry (can use VBG for CO2).

--Need to place patient in the prone position or to perform recruitment maneuvers.

required during each phase of the study will be noted. As per the loss of "clinical stability criteria" stipulation, a subject will be removed from protocol if suctioning becomes necessary more frequently than once per hour (Table 5).

Oxygen desaturation greater than 8 percent (or to less than 88 percent) for greater than 5 minutes is felt to represent an adverse event in this study and will result in study termination and immediate adjustment of the ventilator FiO2 and PEEP as per the orders of the primary care team.

Recruitment maneuvers and prone positioning will not be allowed during the study protocol. Any requirement for these procedures will result in study suspension for that particular subject.

Changes in etCO2 >25% from baseline and lasting greater than 5 minutes will trigger non-invasive blood gas analysis (either arterial or venous, depending on indwelling catheter availability) to evaluate acid-base status. Any change in PCO2 +/- 25% from baseline value, will trigger a proportional adjustment in minute ventilation. Changes in minute ventilation proportional to the change in CO2 will be preferentially initiated through manipulations of respiratory rate, up to 35 breaths per minute. If this upper limit of respiratory rate is reached, the tidal volume (or mean tidal volume) will be increased by 1 cc/kg until the CO2 has returned to baseline. Fifteen minutes after any such ventilator change, another blood gas will be obtained noninvasively to confirm a return to baseline acid-base status. An arterial pH between 7.30 and 7.45 (venous pH of 7.25 to 7.40) will not require a further changes in minute ventilation. If no changes are required for the mechanical ventilator settings during the protocol and oxygenation and end-tidal CO2 measurements remain stable, no extra blood gas analysis (above the baseline, Time 1 and Time 2 blood gases described below) will be performed during the study. All arterial or venous blood gases will be analyzed through the standard hospital laboratory system. All changes to respiratory rate or tidal volume settings will be recorded.

Fluid management will not be subject to protocol during the study period. However, if unexpected changes in the fluid regimen occur, the primary medical team will follow the ALI/ARDS fluid management strategy utilized by our institution, which is

conducted according to the conservative arm of the FACCT trial[23] (Table 6), and this strategy will be continued during the study time frame.

Table 6. FACTT algorithm: Central venous catheter conservative arm.

FACTT ALGORITHM: CVC Conservative

Central Venous Pressure (mmHg)	MAP < 60 mm Hg or on: dopamine >5 mcg/kg/min or any dose of another vasopressor Consider correctable causes of shock first.	MAP ≥ 60 mm Hg AND off vasopressors (Dopamine ≤ 5 mcg/kg/min is *not* a vasopressor)			
		Average UOP < 0.5 ml/kg/hr		Average UOP ≥ 0.5 ml/kg/hr	
		Ineffective Circulation Cold & mottled *with* capillary refill >2 sec (all 3 criteria present)	**Effective Circulation** *Absence* of ineffective circulation criteria	**Ineffective Circulation** Cold & mottled *with* capillary refill > 2 sec (all 3 criteria present)	**Effective Circulation** *Absence* of ineffective circulation criteria
> 13	*1**	KVO IV *3* Dobutamine[A] Furosemide[B.1,2,4]	KVO IV *7* Furosemide[B.1,2,4]	KVO IV *11* Dobutamine[A] Furosemide[B.1,3,4]	KVO IV *15* Furosemide[B.1,3,4]
9-13	Vasopressor[F,†] Fluid bolus[F]	KVO IV *4* Dobutamine[A]	KVO IV *8* Furosemide[B.1,2,4]	KVO IV *12* Dobutamine[A]	KVO IV *16* Furosemide[B.1,3,4]
4-8	*2*	Fluid bolus[C] *5*	Fluid bolus[C] *9*	Fluid bolus[C] *13*	*18* Furosemide[B.1,3,4]
< 4	Fluid bolus[F] Vasopressor[F]	Fluid bolus[C] *6*	Fluid bolus[C] *10*	Fluid bolus[C] *14*	*20* KVO IV *GOAL CELL*

Any subject whose hemodynamic levels fall outside of the clinical stability criteria or who requires a 100-percent increase in vasopressor will be removed from the study. All changes in sedation, fluid management, and pressor levels will be recorded.

Data Collection

Aim 1: Safety and tolerability: The safety of VV will be assessed by comparing the number of times a loss of clinical stability criteria or an adverse event (defined below in Data Safety Monitoring Plan) occurs during each arm of the study. A priori, VV will be deemed to be safe if the occurrence of any event resulting in study termination occurs equally between the two study arms (defined as no more than one extra occurrence during VV mode).

Tolerability of VV will be assessed similarly by comparing the incidence of agitation (Ramsay score of 1) between the two modes. Additionally, tolerability will also be assessed through paired t-test comparisons of the total dose of sedative medications needed during each study arm.

Aims 2, 3, and 4: Efficacy: Identical efficacy data will be collected during three different study time periods: during the 15 minutes prior to start of the study protocol (Time baseline), the last 15 minutes of ventilator mode 1 (Time 1), and the last 15 minutes of ventilator mode 2 (Time 2). These data will include: an arterial blood sample to measure pH, PaO_2, $PaCO_2$, and O_2 saturation; biomarkers of lung injury (IL-6, IL-8, soluble TNF receptor I, IL-1

receptor antagonist, and surfactant protein-D^{24-29} (Table 7); noninvasive lung mechanics, including static compliance (Vt/P_{plat}-$PEEP_{measured}$) and dynamic compliance (Vt/P_{peak}-$PEEP_{measured}$); mean airway pressure; dead space measurement (Vd/Vt measured from $NICO_2$ monitor); and hemodynamic measurements (mean arterial pressure, pulse rate, heart rate variability). An alpha level threshold of 0.05 will determine statistical significance for all efficacy measures.

Protocol Completion and Outcome Measurements

After a total of six hours (three hours on each ventilator mode), the protocol will be complete and the subject will be returned to the ventilator settings he or she had been on prior to the study protocol. All subjects will be monitored for safety continuously through the six-hour study protocol by the study coordinator with continuous EKG, respiratory rate, blood pressure, and pulse oximetry monitoring as per standard of ICU care. In addition, continuous exhaled CO_2 monitoring will be utilized to assure adequate minute ventilation. After the six-hour monitoring on both ventilator settings, a subject's participation in the protocol will be complete; however, subjects who were placed on VV for the second three-hour period will be monitored an additional hour after placement on the previous ventilator settings for tolerability of the return to the baseline ventilator mode. In addition, follow-up data on all patients will be collected twenty-four hours after the protocol to assess the potential of delayed adverse events.

The primary outcome for efficacy will be a significant improvement in PaO_2 measurements during variable ventilation (VV) versus conventional ARDS Net 6 cc/kg ventilation (CV). (See Table 8.) Our power calculations show that 16 patients need to be studied in order to achieve 80% power at an alpha = 0.05 to detect a within-subject 25 mmHg oxygenation difference (with a standard deviation of 25 mmHg) between the VV

Table 7. Biomarkers of Lung injury

Plasma Biomarkers of Lung Injury

Biomarker	Function	Evidence	Kinetics
IL-6	Induces acute phase reactants, leukocyte chemotaxis	**Strongest:** +reduction with protective ventilation[24,25] +assoc w/ outcome[26,27]	Fully reversible change within 1 hour[24] Also change in 12h[25],36h[27], 72h[26]
IL-8	Neutrophil chemotaxis	**Good:** +reduction with protective ventilation[25] +assoc w/ outcomes[26]	Changes seen in 12h[25], 72h[26]
IL-10	Immunmodulator	Fair: +change w/ ventilator strategy in one study[24], not in another[26]. -Not assoc w/ outcome[26].	Trend to reversible change in 1 hour[24]; no change seen after 72h[26].
IL-1 R antagonist	Anti-inflammatory	**Strong:** +Change with protective ventilation[24,4] +Assoc w/outcome[27]	Trend to reversible change in 1 hour[24]; change after 1 and 36 hours[24,27].
TNF a	Imflammatory cytokine, can induce ARDSs	Fair: +small change with injurious ventilation in one study[24], not others[27] -no assoc w/outcomes[27]	Trend to reversible change in 1 hour[24], +change in one hour w/injury[24]
sTNF RI	Released from alveolar epithelium, binds free TNFa	**Strong:** +Change with injurious ventilation[25,27,28] +Assoc w/ outcome[27,28]	+Change in 36 and 72h[27,28]
sTNF RII	Not Released from alveolar epithelium (control), binds freeTNF	Poor: -no change with protective ventilation[27,28]	
SP-D	Surfactant protein, collectin, regulator of innate immunity	**Good:** +Reduced with protective ventilation[29] +assoc w/outcome[29]	Reduced 72h after protective vent[29]

Table 8. Primary and Secondary Outcome Measurements.

Primary Outcome

--Significant improvement in PaO_2 measurements during variable ventilation (VV) versus conventional ventilation (CV).

Secondary Outcomes

--Improvement in physiologic dead space.

--Improvements in static compliance and dynamic compliance.

--Improvements in the biomarkers of lung injury (see Table 7).

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and CV. An effect of this magnitude was seen in three prior human studies using different methods of variable ventilation. [18-20] Secondary outcomes include improvements in:

- Physiologic dead space
- Static compliance
- Dynamic compliance
- Biomarkers of lung injury (Table 7)

Due to the small sample size and predicted nonparametric distribution of these variables, all statistical comparisons of continuous variables will be made with Wilcoxon signed rank testing with statistical significance at $p<0.05$.

A prospective survey of admissions to our institution demonstrated an average of 10 admissions monthly with ALI/ARDS. Speculating that one-half of these patients meet entry criteria, and 20% of these consent for the trial, we anticipate enrolling an average of one patient monthly. Therefore, enrollment should last 16 months.

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RISK ANALYSIS

The primary risks of this study are similar to the potential risks associated with mechanical ventilation, changing ventilator modes, and drawing arterial blood. Risks of mechanical ventilation and changing ventilator modes include, but are not limited to: patient agitation, self-extubation, pneumothorax, airway collapse/mucus plugging, hypotension, arrhythmia, stroke, myocardial infarction, and death. Additionally, unforeseen device malfunction and patient intolerance of the device are potential risks of any new device. Given that this device is a slight modification to a standard ventilator, we expect the probability of either occurrence to be low. Prior studies (Boker A et al., Anesthesiology 2004; 100(3): 608-16 and Taccone et al., presented at the American Thoracic Society International Conference, 2008) of a different method of variable ventilation in human subjects have not shown an increase in adverse events with variable ventilation.

Patients will be monitored continuously by a clinically trained study coordinator/registered respiratory therapist who will supervise all patients through their study protocol session. If at any time a device malfunction might occur, a subject will be immediately placed back on their pre-study ventilator mode and the primary team, as well as the PI, will be notified. Enrollment will be suspended until any malfunction is fully corrected. If any clinical instability criterion or serious adverse event criteria are met, the study session for that patient will be suspended, the primary care team and PI will be notified, and the subject will be returned to the baseline ventilator mode used prior to the study protocol.

Some subjects in this study will have pre-existing arterial catheters for arterial blood drawing as part of their usual clinical care. For these subjects, risks of non-invasively drawing a total of 9ml (3 ml x 3 draws) of blood over 6 hours are minimal. Subjects without pre-existing arterial catheters will have arterial puncture performed for blood drawing. This procedure is routinely performed in the ICU without the need for informed consent. No study has investigated the complication rate for arterial puncture alone, which would be expected to be lower than the complication rates for long-term, in-dwelling arterial catheters. For long-term, in-dwelling arterial catheters, complication rates are: permanent ischemic damage (0.09%), pseudoaneurysm (0.09%), sepsis (0.13%), local infection (0.72%), hematoma (14%), temporary arterial occlusion (19%) (Scheer et al., Critical Care 2002, 6:198-204). Skin will be prepared in a sterile manner and injected with 1-2cc of 1 % lidocaine for local anesthesia prior to arterial puncture. There is a risk of transient, local discomfort during the lidocaine injection.

Given the natural history of patients with ALI/ARDS, there is a moderate likelihood that clinical instability may occur by chance in any patient; therefore, this study is classified as high risk. To ensure optimal safety monitoring and control of risk, the first four subjects enrolled will have ALI (which is less severe than ARDS), only one patient will be enrolled at a time, exposure to the new ventilator mode will be limited to three hours, and patients

will be monitored continuously by the study respiratory therapist as well as the clinical care team with clear stopping rules in place (see below).

Internal Data Monitoring

The PI has overall responsibility for this study; however, subinvestigators with professional clinical training will also have subject monitoring responsibilities. The subinvestigators will conduct real-time data safety monitoring and report to the PI. The subinvestigators include senior pulmonary/critical-care fellow Allan Walkey, MD., and the study coordinator/respiratory therapist Phil Alkana, MA, RRT.

Unanticipated Problems

We will utilize the BUMC definition of unexpected problems (UPs): as an event that is unexpected in severity, nature, or frequency (given the research procedures and the characteristics of the subject population), related or possibly related to participation in the research, and suggests that participation in research places subjects at a greater risk of harm than was previously known or recognized.

Adverse Events

We will utilize the BUMC definition of adverse events (AEs):

- Any untoward or unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

These will be graded as:

- Mild = not requiring treatment
- Serious = requiring a change in care or treatment.

As a guideline, the occurrence of an adverse event will be deemed probably related to the study protocol if it occurs during the experimental VV phase or within one hour from a change in ventilator mode (i.e., within the relevant study time frames). Additionally, probable attribution will be used if the event is felt to be a result of blood drawing during the study protocol. Otherwise, adverse events will be classified as unlikely related to the study pending review by the Safety Committee.

Serious Adverse Events

We will adhere to the BUSM definition of serious adverse event (SAE) as any event that:

- Results in death.

- Is life-threatening.
- Prolongs hospitalization.
- Results in persistent disability.
- May jeopardize the subject's health and may require medical or surgical intervention.

However, as applies specifically to this study, we additionally define the following events as constituting a serious adverse event related to the study if they occur during the relevant study time frame:

- Hemodynamic instability requiring addition of a new vasopressor or greater than 100 percent (doubling) increase in vasopressor dose.
- Self-extubation.
- Decrease in oxygen saturation by more than 8 percent or to a level lower than 88 percent for more than 5 minutes.
- Pneumothorax.
- Myocardial infarction.
- Stroke.

If any serious adverse event, excluding death, occurs in three or more subjects during the relevant study time frame, then we feel that this is a priori greater-than-chance occurrence and the study will be suspended pending further review by the Safety Committee. If one death occurs during the relevant study time frame, then this will also lead to automatic study suspension pending review by the Safety Committee.

Summary of Safety Measures

These are the safety measures we will employ in the VV study:

- The first four patients enrolled in the study will have less severe acute lung injury (ALI).
- One subject will be enrolled at a time.
- There will be a three-hour exposure to the investigational device.
- Clinically trained professional staff, in addition of primary ICU team, will provide real-time continuous monitoring of the subject.
- An independent, expert Safety Committee will provide frequent reviews of the study data.
- Clearly defined event-reporting rules have been established.
- Clearly defined stopping rules have been established.

MONITORING PROCEDURES

Safety monitoring of this study will be performed by a two-member Safety Committee comprised of two attending-level critical care specialists from the BUMC Surgical and Anaesthesia Critical Care Division. These monitors, while experts in critical care, are not investigators associated with this study or the clinical division conducting the study.

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Data Reporting Plan

In the event that any SAE occurs at any time during the 6-hour window of study participation, the participant will be taken off the study and returned to his or her previous ventilator settings. Follow-up and noninvasive safety data collection will continue for 24 hours. The PI will be notified as soon as possible and within 3 hours of any SAE. The independent Safety Committee will be informed about the event within 24 hours. No further participants will be

enrolled until the independent Safety Committee members have assessed the causes of the event (i.e., occurrence within the VV+1 hour time frame) as well as the frequency of all SAEs.

If the event is determined to be unexpected and related to study procedures or intervention, it will be reported to the IRB within 2 days and to the FDA within 10 days (per 21 CFR 803.20 (b)(i)). If the event could reasonably suggest that the study caused or contributed to serious injury or death, it will be reported to the FDA as soon as possible and within 10 working days.

Nonserious AEs will be recorded and reviewed by the independent monitors to assess if the frequency of nonserious AEs is higher than would be expected in this population. These will be submitted to the IRB in the progress report. As an additional safeguard, the Safety Committee will receive each subject's completed case-report forms within 24 hours of protocol completion and will meet after each patient has completed the study protocol to provide independent review for AEs, SAEs, and UPs and to approve continuation of the study.

DEVICE AGREEMENT

Please see the following page for a sample form of the Medical Device Agreement for the Variable Ventilation mode.

MEDICAL DEVICE AGREEMENT

Before participating in the investigation of the use of the Variable Ventilation mode at Boston Medical Center, please read, sign, and return this document to George T. O'Connor, MD, and provide the documentation as listed below.

1. Provide a copy of your curriculum vitae.
2. If relevant, provide a written statement describing your experience in clinical research, including dates, location, extent, and type of experience.
3. If you were involved in an investigation or other research that was terminated, please include an explanation of the circumstances that led to termination in your statement.
4. As a participant in this investigation, you agree to:
    - Conduct the investigation in accordance with this agreement, the investigational plan, the terms of FDA Title 21CFR812 and other applicable FDA regulations, and the conditions of approval imposed by the reviewing IRB or the FDA;
    - Supervise all testing of the device involving human subjects; and
    - Ensure that the requirements for obtaining informed consent are met.

_____ _____

Print name Date

_____

Sign name

LIST OF INVESTIGATORS

Name	Role in study	Reviewed and signed Medical Device Agreement (include date)
George T. O'Connor, MD	Principal Investigator	
Arthur Theodore, MD	Co-investigator	
Allan Walkey, MD	Co-investigator	
Charles O'Donnell, MS, RRT	Co-investigator	

Bela Suki, Ph D	Co-investigator	
Arnab Majumdar, Ph D	Co-investigator	
Phil Alkana, MA, RRT	Study Coordinator	

IRB INFORMATION

The Boston University Medical Centers IRB offices are located at:

560 Harrison Ave

3rd Floor, Suite 300

Main Number: 617-638-7207

Fax: 617-638-7234 (Internally, be careful to dial 8-7234 and not 4-7234)

Email: medirb@bu.edu

Director of IRB

Mary A. Banks, RN, BS, BSN, Director of the Office of the Institutional Review Board and Human Subjects Protection

(617) 638-7207

IRB Chairs

Jonathan Woodson, M.D. (Chair)

(617) 638-8488

Louis Vachon, M.D. (Vice-Chair)

(617) 638-8173

Sanford Auerbach, M.D. (Chair)

(617) 638-8456

James Feldman, MD (Chair)

(617) 414-5972

SITE OF INVESTIGATION

This study will be conducted at the critical care units at Boston Medical Center, including the East Newton Campus at 88 East Newton Street, Boston, MA 02118, and the Harrison Avenue Campus at 840 Harrison Avenue, Boston, MA 02118.

CONSENT FORM

Please see the following pages for a copy of the research consent form.

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RESEARCH CONSENT FORM
Variable Ventilation Study

H-27864 - VARIABLE VENTILATION IN ACUTE LUNG INJURY

Background

This is a research study. Research involves only people who want to take part. This form gives you information about this study. It may contain words or procedure you do not understand.

Your relative's doctor may also be an investigator of this research study. As an investigator, your doctor is interested both in your relative's clinical welfare and in the conduct of this study. Before entering this study, or at any time during the research, you may want to ask for a second opinion about your care from another doctor who is not an investigator in this study. You do not have to participate in any research study offered by your doctor.

Please ask questions about anything that is not clear to you.

"Your relative has a diagnosis of "acute lung injury" or "acute respiratory distress syndrome" and is requiring a breathing machine, or mechanical ventilator, to help him/her breathe. The research team wants to see if a different way of delivering breaths with the mechanical respirator is safe and is better than the way that respirators are usually set to deliver breathing for patients with ARDS and ALI. We plan to study a new method of mechanical ventilation for patients with "acute lung injury" or the "acute respiratory distress syndrome. The current treatment for "acute lung injury" or the "acute respiratory distress syndrome" is a ventilator using a volume of air that is the same for each breath. We plan to test a new method of ventilation, called Variable Ventilation, that delivers breaths that change in size from breath to breath, similar to the breathing of healthy people. In animal testing, this Variable Ventilation has been shown to improve lung function and reduce lung injury compared to the current standard methods of mechanical ventilation.

Purpose

The purpose of this study is to find out whether a new method of mechanical ventilation, called Variable Ventilation, is safe. We will also examine if this new way of giving breaths is well-tolerated and associated with improvements in lung function over our current ventilator practice.

Variable ventilation is a new way to deliver breaths to patients with lung failure that has been found to improve lung function in animal research. The main purpose of this study is to see if this new way to deliver breaths is safe; it is possible that there may be no direct benefit to subjects.

Variable ventilation was developed by a BU Professor of Biomedical Engineering who is connected with this research, but not involved with study subject recruitment or treatment.

What Happens In This Research Study

Your relative will be one of approximately 16 subjects to be asked to participate in this study.

All or part of the research in this study will take place at the following location(s): Boston University Medical Center.

Patients diagnosed with "acute lung injury" or "acute respiratory distress syndrome" who are on a mechanical ventilator are eligible for this study. Relatives of eligible patients will then be contacted to discuss the trial and obtain consent for the study.

Patients who are eligible and whose relatives have provided consent will start the study protocol only when they are 'clinically stable'. This means that a subject's blood pressure, heart rate, level of comfort, blood oxygen levels, and breathing rate on the ventilator must meet strict requirements before entering the study protocol.

The study protocol is as follows:
A subject will receive three hours of ventilation on each of the two methods of mechanical ventilation we will be studying. This means that each subject will participate for six hours in the study. Each subject will spend three hours on their present standard mechanical ventilation method for "acute lung injury" and "acute respiratory distress syndrome" and three hours on the "Variable Ventilation" method we are studying. The order of ventilation methods will be determined by a random process. This means that each subject has an equal chance of receiving standard ventilation or "Variable Ventilation" first, but every subject will receive both methods for three hours. Non-invasive testing will be performed just prior to beginning the trial, and then at the end of each three hour ventilator session.

There will also be a total of three blood draws (3ml, or less than one teaspoon, each) during the study. Some patients enrolled in this study will have catheters already in place to allow non-invasive blood drawing. If an arterial catheter is not already in place, then lidocaine will be used to numb the skin for the blood drawing. The blood will be analyzed for changes that occur on each ventilator mode and stored for five years. All analysis on the stored blood will only relate to this study protocol. No genetic testing will be done.

After the two three hour sessions on each ventilator mode, for a total of six hours of study time, the study protocol will be complete. Subjects' vital signs will be followed for one hour after completion of the study by the study team and the chart will be reviewed 24 hours after the study has been completed. No further involvement in the study will occur for a subject after this time.

Risks and Discomforts

Risks of Switching Ventilator Settings and Variable Ventilation
There is a risk of a change in clinical status from the process of switching ventilator settings. Any change that results in a loss of clinical stability will result in us returning a patient immediately to the mode he or she was on prior to the study and ending the study protocol for this subject. Possible events that might occur during any study of patients on mechanical ventilation and require intervention include change in blood pressure, heart rate, decreased oxygen content, increased agitation, lung collapse, stroke, heart attack, or death.

Arterial Blood Gas Testing
A total of 2/3 of one tablespoon of blood will be drawn for this study in three separate (3ml) blood draws. Arterial blood drawing from a previously-placed arterial catheter is a low risk and routine part of intensive care.

If no arterial catheter is in place, arterial blood draws will be performed. Although arterial blood drawing is a routine task in the intensive care unit, it may present rare risks which include bleeding, hematoma, blood clots, or loss of blood flow to the hand or fingers, or adverse reaction to local lidocaine used to numb the area of blood drawing. There is a risk of discomfort during the lidocaine injection used to numb the skin for the blood drawing. To reduce the risks associated with blood testing, we will perform testing on all subjects to assess adequate blood flow to the hand prior to performing any arterial blood draws.

We plan to store the blood obtained from this study for up to five years for analysis. These samples will only be identified by the study number. We will not perform genetic testing on these samples. If at any time you decide you do not want your blood samples stored, you may contact the principal investigator, Dr. George O'Connor at 617-638-4860.

Subject Confidentiality
We will collect information on your relative for use in the study. We use multiple measures to protect the confidentiality of all subjects. These include collecting a medical record number as the only information that identifies a subject. This medical record number will then link a subject to their data by a special study number. The link between the medical record number and study number will be kept separate from all subject data, including blood samples, and locked in the primary researcher's office. All study data will be password-protected or kept in locked files.

There may be unknown risks/discomforts involved. Study staff will update you in a timely way on any new information that may affect your relative's health, welfare, or your decision to keep your relative in this

study

Potential Benefits

The benefits of participating in this study may be: that the blood oxygen level and lung function may improve during the the 3 hours when your relative if placed on the research breathing method. This benefit is not guaranteed and treatment is not the purpose of this study.. However, your relative may not receive any benefit from participating.

Alternatives

The following alternative procedures or treatments are available if you choose not to give consent for your relative to participate in this study: You may choose not to participate in the study and continue the care as per your primary team of doctors and nurses..

Subject Costs and Payments

There are no costs to you for participating in this research study. You will not be paid to participate in this research study.

Confidentiality

We will use multiple measures to protect the confidentiality of all subjects. Primarily, we will not collect any identifiable data on any subjects. Subjects will receive a study number for identification. With the exception of the institutions named below, only the primary investigator and his study assistants will have access to subject data. This will be kept in a secure manner, password protected and locked in the investigator's office for five years, then destroyed.

Subject's Rights

By consenting to participate in this study you do not waive any of your relative's legal rights. Giving consent means that you have heard or read the information about this study and that you agree to allow your relative to participate. You will be given a copy of this form to keep.

If at any time you withdraw from this study you will not suffer any penalty or lose any benefits to which you are entitled.

You may obtain further information about your rights as a research subject by calling the Office of the Institutional Review Board of Boston University Medical Center at 617-638-7207. If this study is being done outside the United States you can ask the investigator for contact information for the local Ethics Board.

The investigator or a member of the research team will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury while participating in this research, contact GEORGE O'CONNOR at (617) 638-4470 during the day and the on-call intensive care unit physician after hours (reached via pager, BMC operator 617-638-8000).

Compensation for Research Related Injury

If you think that you have been injured by being in this study, please let the investigator know right away. If your part in this study takes place at Boston Medical Center, you can get treatment for the injury at Boston Medical Center. If your part of the study is not at Boston Medical Center, ask the investigator where treatment for injury would be available locally. Boston University Medical Center and the sponsor do not offer a program to provide compensation for the cost of care for research related injury or other expenses such as lost wages, disability, pain, or discomfort. You will be sent a bill for the medical care you receive for research injury if your medical insurance does not pay for your medical care. You are not giving up any of your legal rights by signing this form.

Right to Refuse or Withdraw

Taking part in this study is voluntary. You have the right to refuse to consent for your relative to take part in this study. If you decide to be in the study and then change your mind, you can withdraw from the research. Your participation is completely up to you. Your decision will not affect you or your relative being able to get health care at this institution or payment for your health care. It will not affect you or your

relative's enrollment in any health plan or benefits you can get.

If you choose to take part, you have the right to stop at any time. If there are any new findings during the study that may affect whether you want to continue to allow your relative to take part, you will be told about them as soon as possible.

The investigator may decide to discontinue your participation without your permission because he/she may decide that staying in the study will be bad for you, or the sponsor may stop the study.

Protection of Subject Health Information

You have certain rights related to your relative's health information. These include the right to know who will get your relative's health information and why they will get it. If you choose to enroll your relative in this research study, we will get information about him or her as explained below.

HEALTH INFORMATION ABOUT YOUR RELATIVE THAT MIGHT BE USED OR GIVEN OUT DURING THIS RESEARCH:

- Information from hospital or office health records at BUMC/BMC or elsewhere. This information is reasonably related to the conduct and oversight of the research study. If health information is needed from doctors or hospitals outside of BUMC/BMC, you will be asked to give permission for these records to be sent to the researcher.

- New health information from tests, procedures, visits, interviews, or forms filled out as part of this research study.

WHY HEALTH INFORMATION MIGHT BE USED OR GIVEN OUT TO OTHERS

The reasons we might use or share health information are:
- To do the research described here
- To make sure we do the research according to certain standard set by ethics, law, and quality groups

PEOPLE AND GROUPS THAT MAY USE OR GIVE OUT YOUR RELATIVE'S HEALTH INFORMATION

1. PEOPLE OR GROUPS WITHIN BUMC/BMC

- Researchers involved in this research study

- The BUMC Institutional Review Board that oversees this research

2. PEOPLE OR GROUPS OUTSIDE BUMC/BMC

- People or groups that we hire to do certain work for us, such as data storage companies, or laboratories.

- Federal and state agencies if they are required by law or involved in research oversight. Such agencies may include the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, the Massachusetts Department of Public Health.

- Organizations that make sure hospital standards are met

- The sponsor(s) of the research study, and people or groups it hires to help them do the research

- Other researchers that are part of this research study

- A group that oversees the research information and safety of this study

Some people or groups who get your relative's health information might not have to follow the same privacy rules that we follow. We share your health information only when we must. We ask anyone who gets it from us to protect privacy. However, once the information leaves BUMC, we cannot promise that it will be kept private.

In most cases any health data that is being given out to others is identified by a unique study number and not with your name. So, although in some cases it is possible to link your name to the study data, this is not usually done.

TIME PERIOD FOR USING OR GIVING OUT YOUR HEALTH INFORMATION

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your health information.

YOUR PRIVACY RIGHTS

- You have the right not to sign this form that allows us to use and give out your health information for research. If you don't sign this form, your relative can't be in the research. This is because we need to use the health information to do the research.

- Your relative has the right to withdraw your permission to use or share health information in this research study. If he or she wants to withdraw your permission, they must write a letter to the researchers in charge of this research study.

If they withdraw your permission, we will not be able to take back information that has already been used or shared with others. This includes information used or shared to do the research study or to be sure the research is safe and of high quality.

If you or your relatives withdraws permission, they cannot continue to be in the study.

- Your relative has the right to see and get a copy of the health information that is used or shared for research. However, they may only get this after the research is finished. To ask for this information, please contact the person in charge of this research study.

IF RESEARCH RESULTS ARE PUBLISHED OR USED TO TEACH OTHERS

The results of this research study may be published in a medical book or journal, or used to teach others. However, names or other identifying information will not be used for these purposes without specific permission.